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Role of seasonal influenza in the aetiology of hospitalised acute lower respiratory infections in young children

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Declaration

I, Dr Harish Nair, hereby declare that this thesis has been composed by me. The work included in the thesis is my own unless acknowledged otherwise. I certify that the work has not been submitted for any other degree or professional qualification except as specified.

Dr Harish Nair Date:

Lay Summary of Thesis

Respiratory viruses are a leading cause of chest infections (pneumonia and bronchiolitis) in young children. The global burden of disease due to chest infections related to seasonal influenza virus (influenza) in children is unknown. This thesis aims to estimate the hospital admissions and deaths due to influenza related chest infections worldwide in children younger than five years. This thesis also aims to provide tools for estimating influenza disease burden using data from sentinel surveillance for hospital admissions for chest infections in developing country settings.

The thesis has used data from systematic review of studies published between January 1995 and December 2011 supplemented by unpublished data from two research consortia of 15 and 24 sites based primarily in developing countries to estimate the disease burden due to influenza related chest infections in children younger than 5 years.

The thesis estimates that approximately 1 million children younger than 5 years were hospitalised worldwide in 2008 for influenza related chest infections. The rate of infection was highest in children younger than 6 months. Furthermore, influenza related chest infections resulted in about 21,500 (based on 20 studies) to 115,000 deaths (based on only 1 study) in under-five children that year. The hospitalizations and deaths varied substantially from year to year in any one setting. The disease burden was disproportionately higher in children residing in developing countries (where 90 percent of global under-five population reside) which accounted for 93 percent of all hospitalizations and 99 percent of all influenza related deaths. There are significant gaps in data (particularly mortality related data) from developing countries (especially in the Middle East and Africa).

Influenza related chest infections are common in young children and result in a substantial burden on hospital inpatient services worldwide. Influenza contributes to about 8 percent of all hospitalisations and about 7 percent of all deaths due to chest infections in children younger than 5 years. Sufficient data to precisely estimate the role of influenza in childhood mortality from ALRI are not presently available. Effective use of sentinel surveillance data for disease burden estimation would greatly improve the quality and precision of disease burden estimates (especially those resulting in hospitalisation)

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Full-time education as adult student towards the end of fourth decade of life is not an easy task. This Ph.D. marks the culmination of my university education, which I started more than 20 years ago, collecting numerous degrees and diplomas along the way. I would like to dedicate this thesis to my parents, who always valued education over everything else and encouraged me to always strive harder and achieve success in professional life. I have often heard that behind every successful man is a woman. Surely, this is true in my case. I would never have been able to complete this Ph.D. and achieve success in academia without the constant and invaluable support of my beloved wife, Arti Nair.

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Abstract

Background

Respiratory viruses are a leading cause of acute lower respiratory infections (ALRI) in young children. The role of seasonal influenza virus in childhood ALRI is generally underappreciated. This is because the global burden of disease due to ALRI attributable to seasonal influenza virus in children is unknown. This thesis aims to estimate the global and regional hospital admissions for seasonal influenza-associated ALRI and the possible boundaries for influenza-associated ALRI mortality in children younger than five years. The WHO has developed guidelines for influenza surveillance using severe acute respiratory infections (SARI) sentinel surveillance network. However, data from sentinel surveillance are not routinely used in estimating disease burden in a population. This thesis also aims to provide tools for estimating influenza disease burden using data from SARI sentinel surveillance in developing country settings.

Methods

Incidence data for influenza-associated ALRI (from passive, hospital-based studies) were collected using a systematic review of studies published between January 1, 1995 and October 31, 2010. These data were supplemented by unpublished data from 15 population-based studies that were obtained by forming a consortium of researchers (Influenza Study Group) working in developing countries. The incidence meta-estimates were applied to global and regional population estimates for 2008 to calculate the estimated number of hospitalised influenza-associated ALRI cases that year. The possible bounds for influenza-associated mortality were estimated by combining incidence estimates with in-hospital case fatality ratios and identifying studies with population-based data for influenza seasonality and monthly ALRI mortality.

The data to estimate the incidence of all-cause hospitalised ALRI were collected using a systematic literature review that was supplemented with unpublished data from 24 population-based studies that were obtained by collaborating with research

sites in developing countries (Severe ALRI Working Group). The hospitalised ALRI incidence meta-estimates were applied to global and regional population estimates for 2008 to calculate the estimated number of all-cause hospitalised ALRI cases that year. Data on the proportion of hospitalised ALRI cases that were positive for influenza were collected using a systematic review of the studies published between January 1, 1995 and December 31, 2011. The meta-estimates of the proportion of hospitalised ALRI cases positive for influenza were applied to the estimated number of hospitalised ALRI cases in the year 2008 to estimate the number of hospitalised influenza-associated ALRI cases globally and for the six WHO regions using this alternative method.

The tools for estimating influenza disease burden using surveillance data were developed after a literature review and a survey of 27 end-users (influenza epidemiologists) in 24 countries.

Results

Thirty nine studies (21 from developing and 18 from industrialised regions) satisfying the eligibility criteria, provided data on the incidence of influenza-associated hospitalised ALRI. The incidence is highest in infants in the first six months of life, both in developing as well as industrialised countries. It is estimated that the incidence of hospitalised influenza-associated ALRI in children under the age of five years was about 1.5 (95% CI 1.0 to 2.3) and 1.2 (95% CI 0.9 to 1.6) per 1000 children in developing and industrialised countries respectively. This translates to about 911,000 (95% CI 617,000 to 1.4 million) hospitalisations worldwide due to influenza-associated ALRI in children younger than five years in 2008, 93% of the cases occurring in developing countries (where 90% of the global under-5 population reside). An estimated 21,500 (based on 20 studies) to 115,000 deaths (based on only 1 study) in under-five children were attributable to influenza-associated ALRI in 2008. Incidence and mortality varied substantially from year to year in any one setting.

Eighty five studies (61 from developing and 24 from industrialised) reported incidence of hospitalised ALRI in children aged 0 to 4 years. It is estimated that

about 11.3 (95% CI 9.5 to 13.5) million episodes of ALRI resulting in hospitalisation occurred worldwide in children aged 0 to 4 years in 2008, 92% of these occurring in developing countries. Twenty three studies (19 from developing and 4 from industrialised) reported data on proportion of hospitalised ALRI cases testing positive for influenza using laboratory tests. The estimated proportion of influenza-positive hospitalised ALRI cases was about 5.0 (95% CI 3.6 to 7) percent and 8.4 (95% CI 4.2 to 16.7) percent in developing and industrialised countries respectively. This translates to about 772,000 (95% CI 343,000 to 1.8 million) cases of influenza-associated hospitalised ALRI in children younger than five years worldwide in the year 2008.

A manual (targeted at developing countries) describing the methods to estimate the disease burden associated with seasonal influenza using the various surveillance data was developed after considering the results of the preliminary survey. An electronic tool (based on a spread sheet model) to help the end-users (epidemiologists at sentinel surveillance sites and Ministries of Health) to estimate the disease burden at local and national levels was developed as an adjunct to the manual. The manual along with the electronic tool were piloted at three different sites in two developing countries (India and Ghana) and feedback from the end-users was obtained to make the version more user-friendly. The final draft of the manual along with the tool has been submitted to the WHO for final clearance. The member states and the WHO Eastern Mediterranean Regional Office decided to adopt the manual and in the first instance estimate the influenza disease burden in 8 member states having the requisite data for undertaking disease burden estimation.

Conclusions

Influenza is a common pathogen identified in children with ALRI and results in a substantial burden on hospital inpatient services worldwide. There are significant gaps in published data from developing countries (especially the African and Eastern Mediterranean regions of the WHO). Sufficient data to precisely estimate the role of influenza in childhood mortality from ALRI are not presently available. Effective use of sentinel surveillance data for disease burden estimation would greatly improve the

quality and precision of disease burden estimates (especially those resulting in hospitalisation). Improved disease burden estimates (particularly at the national level) would inform policy makers and national governments in formulating immunization policies for vaccinating high-risk groups, and planning annual requirements for vaccines and anti-viral drugs against seasonal influenza.

Chapter 1. Introduction

1.1. Acute lower respiratory infections

Acute lower respiratory infections (ALRI) comprising mostly clinical pneumonia and bronchiolitis are the leading cause of morbidity and mortality in young children. Rudan and colleagues estimated that globally 156 million new episodes of ALRI occurred in the year 2000 of which 151 million (about 97%) were in developing countries (Rudan et al., 2008). It is estimated that approximately 1.57 and 1.39 million children died as a result of ALRI in the year 2008 and 2010 respectively, 99 per cent of these in developing countries (Liu et al., 2012, Black et al., 2010). ALRI disease burden is disproportionately high in developing countries where 90% of the global under-five population lives. Presently, there are no systematically established global estimates of the incidence of severe ALRI (hospitalised or otherwise) in children less than 5 years of age. The best estimates are those by Rudan and colleagues (based on six studies) which indicate that 6 to 12% of all ALRI cases may progress to severe disease and require hospitalization (Rudan et al., 2004).

The three major causal agents of ALRI in young children (28 days – 59 months) are *Steptococcus pneumoniae*, *Haemophilus influenzae* type B (HiB) and Respiratory Syncytial Virus (RSV). Viral aetiologies are responsible for the majority of episodes of ALRI. *Steptococcus pneumoniae* and HiB, the leading bacterial causes are together estimated to be responsible for 13% and 27% of all ALRI and severe ALRI episodes respectively; and 50% of ALRI associated mortality in children below the age of 5 years (O'Brien et al., 2009, Watt et al., 2009). Published studies have shown that RSV is the most important viral pathogen isolated in ALRI cases worldwide (Weber et al., 1998, Simoes, 1999) although there were no precise RSV-associated ALRI global burden estimates prior to the start of this doctoral thesis. In order to pilot the methods for data collection and analysis used for this thesis, an RSV Study Group (comprising investigators from developing countries) was established. A systematic review of published literature along with unpublished data from the RSV Study Group indicate that about 22% and 30% of all ALRI and severe ALRI episodes respectively; and 3 to 9% of all ALRI deaths in children aged below five

years are attributable to RSV (Nair et al., 2010). Thus, RSV is the single largest cause of ALRI in young children.

Among viral aetiologies, apart from RSV, seasonal influenza viruses (type A and B), human metapneumovirus (hMPV), parainfluenza viruses (type 1, 2 and 3), and adenovirus have been found to be other important causes of childhood ALRI (Straliotto et al., 2002, Karaivanova, 1995, Kusel et al., 2006, Graham, 1990). It is now generally believed that a substantial proportion of ALRI in children are mixed infections (a combination of viral or mixed viral-bacterial infections). This evidence of mixed viral-bacterial infection has been recorded in up to 45% of cases of community-acquired pneumonia in children (Lahti et al., 2009, Juven et al., 2000, Tsolia et al., 2004, Cilla et al., 2008, Hamano-Hasegawa et al., 2008, Nascimento-Carvalho et al., 2008, Samransamruajkit et al., 2008, Cevey-Macherel et al., 2009, Wolf et al., 2010). Not surprisingly, the most common combination in mixed viral bacterial infections is that of *Streptococcus pneumoniae* with various respiratory viruses. In a study from the Gambia, 33% of children with pneumococcal pneumonia also had evidence of a respiratory virus infection diagnosed using viral culture or serologic tests (Forgie et al., 1991). Johnson and colleagues demonstrated in a study from Nigeria that about 16% of all community-acquired pneumonia cases were mixed viral bacterial in origin. (Johnson et al., 2008).

Over the past decade, *Haemophilus influenzae* type B (HiB) and pneumococcal conjugate vaccines (PCV) have been introduced into immunisation programmes in developing countries. It is generally believed that as the coverage of these vaccines increases, the relative proportion of respiratory viruses as causes of childhood ALRI will increase. Additionally, it is very likely that the landscape of bacterial pathogens will change due to replacement by non-vaccine serotypes in PCV vaccinated population. The emergence of severe acute respiratory syndrome (SARS), avian influenza A (H5N1), and influenza A (H1N1)pdm09 has re-emphasised the important role of respiratory viruses as contributors to severe ALRI. New respiratory viruses such as human metapneumovirus, corona viruses NL 63 and HKU1, and human boca virus have been discovered during the past decade. In the next few years, the focus of international scientific community, agencies like the Bill and

Melinda Gates Foundation and the World Health Organization is increasingly likely to be on viral bacterial interactions and the synergistic effect introduction of a vaccine against viral pathogens (e.g. influenza vaccine) would have on pneumonia disease burden reduction in the presence of a sustained high coverage for *Haemophilus influenzae* type B and pneumococcal conjugate vaccines in developing countries.

Influenza has long been considered as a disease of the elderly because of the high incidence, hospitalisation and mortality rates in those over 60 years of age (Iskander et al., 2007). It was considered to be serious only in those children with underlying chronic medical conditions who were at a higher risk of developing complications. However, studies over the past decade have shown that the burden of disease due to influenza in healthy young children is as much as in the elderly if not more (Thompson et al., 2004, Brotherton et al., 2004, Neuzil et al., 2002, Poehling et al., 2006). Moreover, the incidence rates for influenza in childhood are inversely related to the age of the child, the rate being highest in infants in the first year of life (Poehling et al., 2006, Moore et al., 2006). Brotherton and colleagues estimated that in Australia influenza-associated mortality rate in children is only one-tenth of those aged over 60 years (0.1 compared with 1.1 per 100000) (Brotherton et al., 2004). Presently, there are no estimates of the global incidence and mortality due to seasonal influenza-associated ALRI in young children.

1.2. Influenza virus

Influenza viruses belong to the family orthomyxoviridae and are classified as A, B or C. They are negative sense single stranded RNA viruses that contain 8 separate gene segments of RNA. The segmented nature of the genome is important because it allows genetic re-assortment, a process by which different influenza viruses co-infecting the same host cell can exchange genes, resulting in progeny viruses containing genes from both parent viruses. Influenza A and B viruses are responsible for seasonal epidemics of what we generally think of as influenza illness, while influenza C viruses cause sporadic cases of mild common cold-like illness. Influenza A viruses are further categorized into subtypes (e.g. H1N1 or H3N2) on the basis of

surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA) (Figure 1). While antigenically distinct B strains are currently circulating globally, these are not different enough from each other genetically to be called subtypes. Influenza B viruses are rather currently grouped into two lineages (Victoria and Yamagata) but not sub-typed. Influenza A viruses circulate among a diverse range of host species, including birds, swine, horses and humans but B viruses only infect humans. The large pool of genetically distinct influenza A viruses circulating among animal species serves as a source of "novel" viruses to which humans have little or no immunity. The introduction of these viruses into human populations is responsible for periodic worldwide influenza pandemics. At the level of individual patients both influenza A and B viruses cause clinically indistinguishable disease.

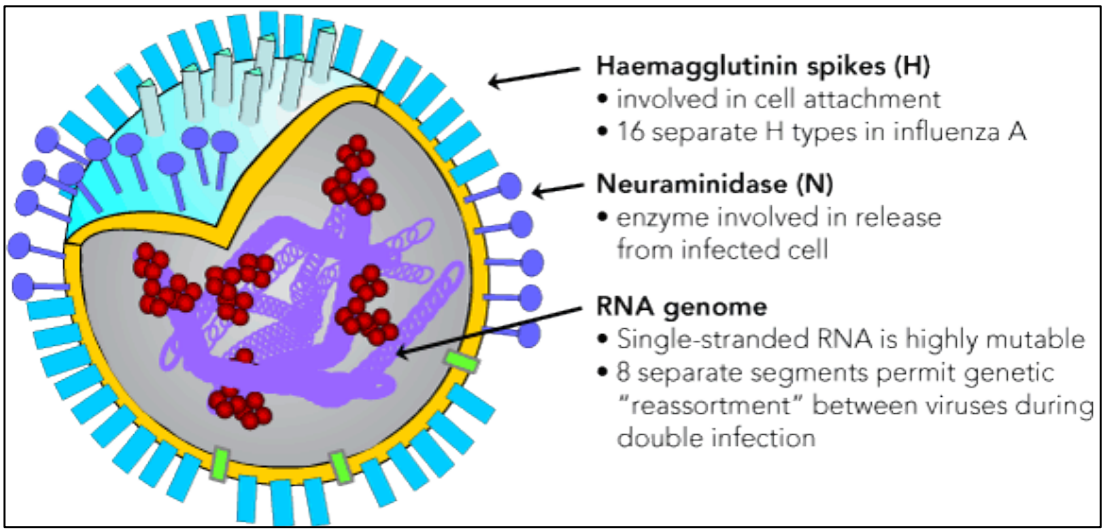

Figure 1: Diagrammatic representation of the human influenza virus

Pandemic influenza refers to a global epidemic of influenza that occurs when an influenza A virus bearing novel HA or HA/NA combination emerges and spreads. Four influenza pandemics have occurred in the past century, the most recent being in 2009-10 (Figure 2). The first pandemic of the twentieth century occurred in 1918-19, with the emergence and spread of influenza A(H1N1), or "Spanish flu" which resulted in more than 20 million deaths worldwide , more than the total casualties of World War I. In 1957-58, the emergence of influenza A (H2N2) led to a pandemic of

"Asian flu". The third pandemic occurred in 1968-69 in association with the emergence of influenza A (H3N2), or "Hong Kong flu". The fourth and most recent pandemic occurred with the emergence of influenza A(H1N1)pdm09 or "swine flu" .

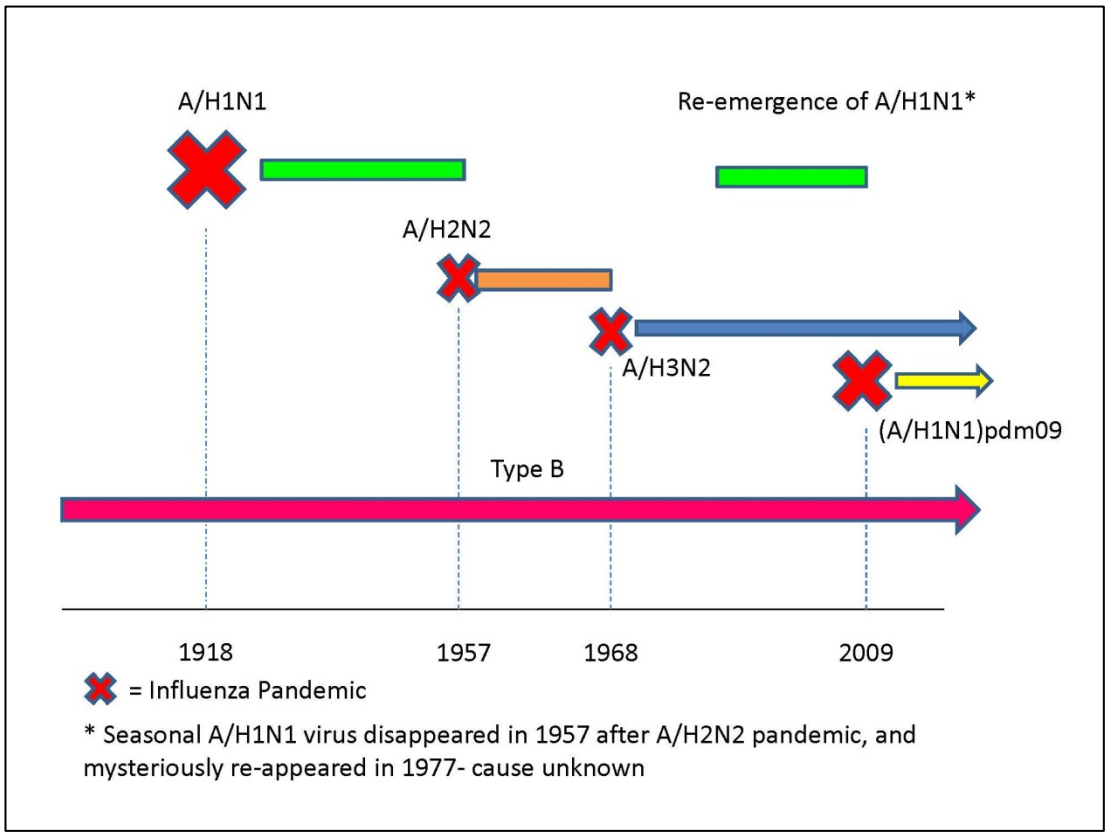

Figure 2: Influenza pandemics since 1900

Antigenic change is one of the hallmarks of influenza viruses and occurs through one of two distinct mechanisms: antigenic drift and antigenic shift. Antigenic drift refers to a process by which point mutations in the RNA genome of influenza virus result in antigenic variants. When these changes result in a survival advantage for the virus, the new antigenic variant can become the predominant circulating strain. As an increasing number of individuals within the population develop antibody against the new circulating strain, selective pressure favours the emergence of one of the variant strains, which then becomes the next predominant strain in an on-going global

process. Each new antigenic strain typically predominates in circulation for a few years before it is displaced by the next emerging strain.

Antigenic shift resulting in a global pandemic occurs by one of the two mechanisms: genetic re-assortment between animal and human influenza viruses; or a direct jump from animal species to humans of a virus that has acquired the ability to easily spread from human-to-human. In the former, genetic re-assortment can occur if a suitable host such as swine is co-infected by both human and non-human (animal) influenza viruses allowing the two viruses to intermingle their genetic material. This mechanism appears to have resulted in the 1957 influenza A(H2N2), 1968 influenza A(H3N2), and influenza A(H1N1)pdm09 pandemic viruses. The second mechanism is less well understood but likely occurs when animal influenza viruses that generally do not infect humans develop mutations that allow them to more easily infect humans. Antigenic shift occurs relatively infrequently. It is as yet not very clear if the 1918 influenza A (H1N1) pandemic virus was a genetic re-assortment or an adaptive mutation of hitherto avian influenza virus (Gibbs and Gibbs, 2006, Taubenberger et al., 2005).

1.1.1. 2009 Influenza pandemic

The first pandemic of this century occurred with the emergence of influenza A(H1N1)pdm09 or “swine flu” with the US Centers for Disease Control and Prevention (CDC) reporting the detection of two cases in children in Southern California, USA on April 21, 2009. The pandemic may have begun sometime earlier in March when health authorities in Mexico started detecting a surge in influenza like illness (ILI) in the country, later confirmed to be caused by the same virus detected by the CDC. Over the next couple of weeks, the pandemic which started in North America spread rapidly across the world. Two hundred and fourteen countries from all over the world reported laboratory confirmed cases of influenza A(H1N1)pdm09 to WHO (WHO, 2010). During the pandemic period (21 April 2009-10 August 2010), around 18500 deaths were reported to have been caused by this disease. This is likely to be a gross underestimation as diagnostic specimens are not always collected from fatal cases and viruses might no longer be detectable by the time of

hospital admission/death in some people. Dawood and colleagues estimate that globally there were over 200,000 respiratory deaths (range 106,000 to 396,000) and an additional 83,000 cardiovascular deaths (range 46,000 to 180,000) associated with influenza A(H1N1)pdm09 (Dawood et al., 2012). Presently, there are no reliable estimates of the global incidence of influenza A(H1N1)pdm09 associated respiratory infections in children or of the excess burden of disease due to the pandemic virus over the seasonal influenza virus during this period.

1.2. Laboratory diagnosis of influenza

A presumptive diagnosis of influenza can be confirmed by one of the four approaches: virus isolation, detection of viral proteins, detection of viral RNA, or serological diagnosis. In children (and in adults), influenza virus is isolated most often from respiratory secretions that are obtained by nasal swab, throat swab, or nasal aspirate within the first few days of illness. In young children, viral titres are higher and viral shedding may continue for several more days than in adults. Viral culture is considered to be the “gold standard” because it has high specificity and high sensitivity, although the sensitivity is lower than with Polymerase Chain Reaction (PCR) assay. Specimens should be transported to the laboratory using a transport media and on wet ice and inoculated into eggs or tissue culture (including Madin-Darby Canine Kidney (MDCK) Cells and primary Rhesus monkey kidney (RMK) cells). Virus can be detected from cell culture from about two thirds of infected patients within three days (of inoculation) and almost all with positive specimens in fewer than seven days. The technique is time consuming, expensive and requires special handling all of which limit its use in routine clinical settings.

One of the important advances in influenza diagnosis is the introduction of rapid diagnostic assays (Cox and Subbarao, 1999). The expression of viral antigens can be detected by immunofluorescence within 24 to 48 hours after infection (Espy et al., 1986). Tests for influenza antigens on exfoliated nasopharyngeal cells using direct or indirect immunofluorescence have shown variable sensitivity (40-100%) and specificity (86-99%) (Rawlinson et al., 2004) (Table 1) . Several rapid diagnostic kits

that rely on immunoassay or detection of viral nucleic acid using PCR assay are commercially available (Table 1). These rapid diagnostic kits can be used for point-of-care testing and can provide a result within 30 minutes. PCR based assays offer high sensitivity and specificity, although contamination of specimens is a concern (Stockton et al., 1998) (Table 1). The optimal use of rapid diagnostic assays in the clinical setting is a point of concern mainly because it is still not practical to test all patients and that too within the first 48 hours of onset of illness mainly because of cost involved and poor access to care especially in developing countries.

Table 1: Comparison of the sensitivity and specificity of various diagnostic assays against viral culture (gold standard)

Diagnostic Assay	Sensitivity (%)	Specificity (%)
Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) (Templeton et al., 2004)	100-110 *	93
Direct immunofluorescence (DFA) (Mahony, 2008)	70-100	80-100
Indirect immunofluorescence (IFA) (Rawlinson et al., 2004)	90-100	100
Enzyme-linked Immunoassay (EIA) (Mahony, 2008)	70-75	90-95
Rapid Point of Care (POC) Tests		
Quickvue / Directigen (Grijalva et al., 2007a, Bellei et al., 2003)	47-78	94-99

* Sensitivity has been computed using viral culture as gold standard. If more samples test positive for seasonal influenza using RT-PCR compared to when simultaneously tested using viral culture, the sensitivity for RT-PCR based test will exceed 100%

Diagnostic Assay	Sensitivity (%)	Specificity (%)
Z-stat Flu (Rawlinson et al., 2004)	65-77	77-97

The US CDC has introduced the Taqman Array Card (TAC) across its field sites globally after the 2009 influenza pandemic (Fields, personal communication). The premise of TAC is to be able to test for multiple pathogens from a single specimen; at this point only respiratory specimens have been used. This offers a significant advantage when specimen volumes are minimal; and also decreases the costs and turnaround time for results. Currently, the utility of TAC is being assessed at International Emerging Infections Program (IEIP) field sites along with National Influenza Centres (NIC) in developing countries. TAC has high sensitivity and specificity in general though this varies with pathogen (Table 2). The widespread use of TAC can help understand the aetiology of acute lower respiratory infections especially those that are viral in origin and also estimate the burden of co-infections.

Table 2: Sensitivity and specificity of Taqman Array Cards (TAC) specific pathogen assays compared to individual qPCR assays using a Ct [†] cut-off value of 43 in nasopharyngeal / oropharyngeal swabs

Target	Sensitivity (95% CI)	Specificity (95% CI)
Influenza A	92 (80 to 100)%	99 (96 to 100)%
Influenza A – H1	100 (100 to 100)%	100 (100 to 100)%
Influenza A – H3	83 (65 to 100)%	99 (96 to 100) %
Influenza B	100 (76 to 100)%	100 (100 to 100)%

[†] A cycle threshold (Ct) (the PCR cycle where the fluorescent signal exceeds that of the threshold value) <43 was scored as a positive result

Target	Sensitivity (95% CI)	Specificity (95% CI)
Respiratory syncytial virus	100 (100 to 100)%	97 (94 to 100)%
Human parainfluenza virus (Type1)	100 (100 to 100)%	100 (100 to 100)%
Human parainfluenza virus (type 2)	79 (55 to 100)%	96 (92 to 100)%
Human parainfluenza virus (type 3)	95 (86 to 100)%	100 (100 to 100)%
Human metapneumovirus	95 (85 to 100)%	99 (96 to 100)%
Rhinovirus	98 (93 to 100)%	91 (84 to 97)%
Enterovirus	100 (100 to 100)%	92 (86 to 98)%
Human paraechovirus	100 (100 to 100)%	100 (100 to 100)%
Adenovirus	97 (90 to 100)%	100 (100 to 100)%

In spite of the emerging popularity of rapid diagnostic tests, viral culture remains important because the characterization of viral isolates yields more genetic data than any other technique, and the information provided is critical for annually updating the influenza vaccine and for identifying the potential pandemic viruses. Another technique, which was popular until the early 1990s is serologic diagnosis of influenza which requires demonstration of a four-fold or greater increase in antibody titre between paired acute and convalescent sera obtained at least 2 weeks apart. Measurement of antibody titre in a single sample is of limited value except in cases where infection with a novel influenza virus is in question (Rennels et al., 2002). Measurements of haemagglutination inhibition (HAI) antibodies are used most commonly for serology, although complement fixation testing is also used. Presently, serologic diagnoses are only used in epidemiologic studies.

1.3. Natural history of disease

Influenza infection in children can manifest itself in varied presentations (Figure 3). It commonly presents as a mild "influenza like illness" in which case patients may complain only of fever, myalgia, malaise, headache and sometimes vomiting and diarrhoea. In children, it could also present or progress to an upper respiratory infection (URI) presenting with non-productive cough, rhinitis and sore throat. In infants, rhinitis may be the only respiratory manifestation of the disease. One of the important complications of influenza-associated URI is acute otitis media (AOM) (Heikkinen et al., 1999, Chonmaitree et al., 2008). It is estimated that 3 to 5 per cent of children experience influenza-associated AOM annually (Neuzil et al., 2002, Ruuskanen et al., 1989). In some cases it can also result in acute laryngotracheobronchitis (Croup) (Principi et al., 2004). Influenza infection can also lead to viral pneumonia and less commonly bronchiolitis (both of which constitute ALRI). Typically the course of influenza-associated ALRI progresses over a few days with worsening of the symptoms. Influenza-associated ALRI can be complicated by secondary bacterial pneumonia, usually attributable to *Streptococcus pneumoniae* and occasionally caused by *Staphylococcus aureus* or *Streptococcus pyogenes* (Klugman et al., 2009, O'Brien et al., 2000, Reed et al., 2009, van der Sluijs et al., 2010), although in children *S pneumoniae* is by far the commonest cause. Secondary bacterial pneumonia has been responsible for majority of deaths in all age groups during the 1918 and 1957 influenza pandemics. This secondary bacterial pneumonia generally occurs after a period of improvement of the primary illness with recrudescence of fever associated with symptoms of pneumonia. Thus, a 10 to 30 per cent increase in the number of antimicrobial courses prescribed to children in a defined study population in the US has been recorded during the influenza season (Neuzil et al., 2000). Influenza-associated illness may be complicated infrequently by cardiopulmonary complications like myocarditis (Coffin et al., 2007), and exacerbation of asthma. (Miller et al., 2008); neurological complications like Guillain-Barre Syndrome (Tam et al., 2006, Sivadon-Tardy et al., 2009, Sivadon-Tardy et al., 2006), febrile seizures (Chiu et al., 2001, Lester-Smith et al., 2009), transverse myelitis, postinfectious encephalitis and encephalopathy

including Reye's Syndrome (Togashi et al., 2004, Kasai et al., 2000, Morishima et al., 2002, Okabe et al., 2000). It has also been rarely associated with myoglobinuria accompanying myositis rarely progressing on to renal failure (Lester-Smith et al., 2009, Buss et al., 2009)- more commonly seen after an infection of influenza B rather than influenza A.

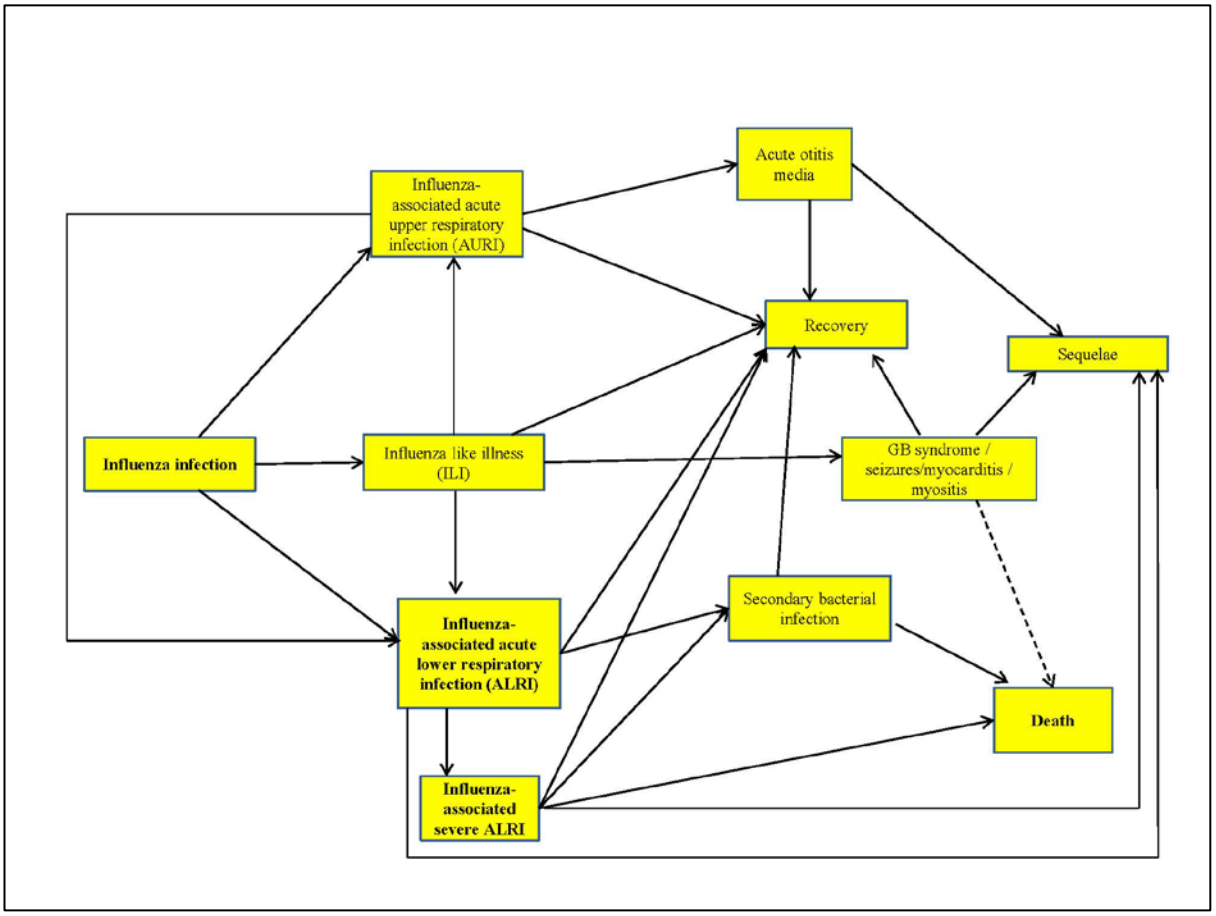

Figure 3: Natural history of disease due to influenza virus infection in children

Viral pneumonia (particularly those associated with a secondary bacterial pneumonia) have a high mortality rate (Rennels et al., 2002). However, available literature from industrialised countries seems to suggest that the case fatality ratio (CFR) and the absolute number of deaths attributable to influenza is higher in elderly population (aged above 65 years) than in young children. The CFR in US children has been estimated to be about 3.8 per 100,000 cases (Glezen, 1996). However, this is likely to be much higher in developing countries where access to and quality of

hospital care is generally limited and variable. Post influenza encephalitis or encephalopathy has a high CFR and survivors are often severely neurologically damaged. Since 1994, more than 200 cases of severe, acute necrotizing encephalopathy associated with influenza infection have been reported in young Japanese children (Kasai et al., 2000, Morishima et al., 2002, Togashi et al., 2004). However, a causal relationship has not yet been established.

1.4. Current influenza disease burden estimates (modelling approaches)

Estimating the burden of influenza on hospitalizations and deaths is very challenging. Severe clinical outcomes are often caused by secondary bacterial infections or exacerbation of underlying chronic conditions and the primary infection may be unrecognised. Additionally laboratory confirmation of influenza infection is rarely conducted (Viboud et al., 2006). As a result, most influenza related hospitalizations and deaths are not attributed to influenza on discharge forms and deaths, thus necessitating the use of statistical models to assess the true burden of influenza on health. Traditionally, for temperate countries, estimates of the impact of a particular influenza epidemic relied on two approaches- either the comparative method or the Serfling method. The former is based on identifying periods without influenza activity to generate a model of expected winter baseline deaths (or cases) which then is used to estimate the excess deaths or excess cases by either subtracting this baseline from the observed number of deaths or hospitalisations during influenza epidemics (Collins et al., 1930, Simonsen et al., 1998). The latter on the other hand, is based on setting a baseline for excess number of events by fitting a linear regression function to the data of the period assumed to have low virus circulation (Serfling, 1963, Simonsen et al., 2005). One major limitation of both these methods is that a number of respiratory viruses like RSV and hMPV co-circulate during the influenza season and a large proportion of ILIs may in fact be caused by these viruses. Extremes of temperature, especially cold spells, that are likely to cause substantial mortality, is an important confounder in these syndromic surveillance models (Donaldson and Keatinge, 2002). The US CDC developed a Poisson regression model to simultaneously estimate both age-specific influenza subtype-

specific mortality as well as RSV-associated mortality (Thompson et al., 2003) in the United States. Instead of using the observed numbers of deaths and excess deaths to define influenza epidemics, data from virological surveillance were used and excess mortality was calculated as the difference between the expected values when the observed proportion of virus isolations is fitted and the values when no virus circulation is assumed. In this approach the errors introduced by subjectively defining periods of high and low influenza virus activity can be minimized. A modification of the model was developed to provide estimates of influenza-associated hospitalizations in the United States (Thompson et al., 2004). The key assumptions, strengths and limitations of these approaches are outlined in Table 3.

Table 3: Key features of the common statistical modelling approaches to estimate influenza disease burden

Modelling approach	Data used	Assumptions	Strengths	Limitations
Comparative	Weekly, monthly or annual time-series of mortality	▪ Months or years without influenza activity are considered baseline (e.g. peri-influenza period, right before influenza activity starts, can be used as baseline) ▪ Influenza attributable deaths= deaths during the epidemic period minus deaths during baseline periods	Extremely simple	▪ Need to identify baseline period prior to modelling ▪ Imprecise, especially if annual data are used and has a tendency to underestimate influenza burden
Serfling	Monthly or weekly time-series of mortality	▪ Periods without influenza activity are used to generate a model baseline of expected winter deaths ▪ Fits a seasonal regression to deaths in non-influenza periods ▪ Impact of a particular influenza epidemic is estimated as the number of excess deaths above a seasonal baseline ▪ Assumes that the seasonal baseline accounts for the	▪ Does not require virological data where seasonality of influenza virus has been previously documented ▪ Adjusts for the impact of non-influenza respiratory viruses through seasonal baseline	▪ Need to identify baseline period prior to modelling ▪ Not suited to studying disease burden of seasonal influenza in tropics where there is no well demarcated influenza season ▪ RSV activity is known to vary annually and is not suited to estimate influenza morbidity and mortality in young children (<5 years) where the burden of RSV is highest (and therefore the estimates are likely to be confounded)

Modelling approach	Data used	Assumptions	Strengths	Limitations
		burden of non-influenza, respiratory pathogens including, RSV, and has no annual variation		
Poisson	Monthly or weekly time-series of mortality; monthly or weekly time-series of viral activity	▪ Virological surveillance data are used to guide disease burden models ▪ Assumes a proportional relation between virus activity and the number of hospitalisations or deaths attributable to influenza	▪ Can be used to simultaneously study the burden of different influenza subtypes (if such data from virological surveillance are available), and RSV ▪ Can be used to estimate influenza disease burden in tropical and subtropical regions	▪ Requires excellent virological surveillance data since weekly/monthly increases in viral activity are linked to weekly/monthly increase in influenza-associated deaths ▪ Does not allow for variations in the severity of influenza A strains between years; better suited to estimate an average burden across many years rather than the burden in an individual year

The above methods are however not valid in the tropics where influenza viruses circulate throughout the year without a clearly demarcated and predictable epidemic peak or periods of viral activity. Assessments based solely on peak epidemic periods will underestimate the burden of influenza (Simonsen, 1999). Wong and colleagues used a modification of the Serfling-Poisson model proposed by Thompson (Thompson et al., 2004) to estimate influenza-associated hospitalisations and mortality in Hong Kong by defining periods of influenza predominance and baseline periods using data from virological surveillance (Wong et al., 2004, Wong et al., 2006).

Other approaches to estimate the morbidity and mortality due to influenza which are seldom used include:

i. Peri-seasonal and summer seasonal rate-difference models which are based on the comparative method (Izurieta et al., 2000, Barker and Mullooly, 1980, O'Brien et al., 2004, Mullooly et al., 2007)

ii. Cyclical regression model which has the Serfling method as its underlying basis (Simonsen et al., 1997)

iii. Autoregressive integrated moving average (ARIMA) model which uses a comparison of the ratio of pneumonia and influenza deaths to all-cause mortality during the epidemic and non-epidemic periods (Choi and Thacker, 1981)

Because the models based on the comparative method are simple and require fewer assumptions, they have been used in a wide-range of situations. For example, these models have been used to make estimates of influenza-associated mortality by 5-year age intervals (Thompson et al., 2006). In the case of tropical and sub-tropical countries which lack definitive seasonality with regard to influenza virus activity, any predictive model based on Serfling or Poisson regression to estimate influenza-associated mortality in young children would require at the least viral isolation data (to define periods of influenza activity), denominator based data on all-cause or ALRI mortality in young children by month, as well as weekly data on temperature

and humidity. Good quality all-cause / ALRI mortality data from vital registration systems may not be available in most developing countries (Rudan et al., 2005) and are unlikely to be available by week / month.

Like the morbidity and mortality burden, the socio-economic burden of influenza is dependent on disease severity (which varies from year to year), but in general, influenza is associated with substantial socioeconomic consequences on families, healthcare services and society (Principi et al., 2003, Neuzil et al., 2002). Socioeconomic impact can be estimated by estimating the direct and indirect cost of influenza illness in a child. The direct costs include those related to physician visits, medications and hospitalisation. Keren and colleagues demonstrated that the mean total cost of hospitalisation (direct cost) for an episode of influenza in Philadelphia, US was \$13159 [‡] (interquartile range \$3896 to \$10882) with a small number of high cost hospitalizations raising the mean cost above 75th percentile (Keren et al., 2006). Almost half of the children hospitalised for influenza had one or more chronic medical conditions (asthma, chronic lung diseases, cardiac disease, immunosuppression, haemoglobinopathies, chronic renal disease etc.) recognised by the Advisory Committee on Immunization Practices in the US as risk factors for severe influenza. However, the mean total cost of hospitalisation for a patient admitted to ICU was \$39972 – more than 5 times the mean total cost (\$7030) for patients cared for exclusively on the wards. The high direct cost of influenza also extends to children managed in the community. A population-based prospective study in 234 Australian children aged under 5 years showed that outpatient laboratory confirmed influenza incurred almost 3 times the cost (AU\$904) compared to laboratory confirmed RSV (AU\$304) (Lambert et al., 2008a). It must however be noted, that cost data are country-specific and not directly comparable. In general, cost of ALRI hospitalisation (per episode) in industrialised countries is several magnitudes higher than those in developing countries (unpublished data).

[‡] The mean is higher than the 75th percentile, as some of the cost data are highly skewed towards the extreme (higher end).

The indirect economic burden, including absence from school, secondary infection of household contacts of sick children leading to parental illness, missed work days and transmission of influenza to the work place, overshadows the direct costs of paediatric influenza and has not been adequately assessed in the past. In a study published a few years ago, Tsolia and colleagues found that for each child with influenza, a mean of 1.34 work days were lost by the parents to care for the sick child and a further 0.36 days for their own illness (Tsolia et al., 2006). The secondary bacterial infection rate for influenza, however, was significantly higher than for other respiratory viruses (17 compared with 11%; $p<0.0001$), suggesting a higher rate of interfamilial spread compared to other infections. The indirect burden was further illustrated in a study by Esposito and colleagues that compared influenza with RSV infection in children aged less than 15 years presenting to the emergency department for acute conditions (Esposito et al., 2005). The study demonstrated that previously healthy children with influenza missed more school days than RSV-positive children (12 compared with 5 days, $p=0.003$). Household contacts of influenza-positive children had significantly higher incidence of influenza like illness, and absence from work or school compared to those of RSV-positive children.

1.5. Severe Acute Respiratory Infection Surveillance

The Global Influenza Surveillance Network (GISN) – now rechristened, Global Influenza Surveillance and Response System (GISRS) – has been performing virological surveillance for influenza since 1952. The GISRS consists of 130 National Influenza Centres (NICs) around the world that collect and test clinical specimens for influenza virus. In the recent years (more particularly following the 2009 pandemic), the WHO and the global community recognised the need to expand influenza surveillance and include epidemiological information to complement the virological data collected by GISRS. The lack of any established surveillance for severe influenza related disease in most countries and the resulting absence of historical data and limited the ability to evaluate the severity of the pandemic in the context of previous seasons. The lack of a pre-existing international mechanism for sharing epidemiological data presented challenges to understanding global patterns

of influenza disease transmission. And, finally, the non-standardised approach to data collection and outbreak investigation restricted to such eventualities resulted in data that were often incomplete and that could not be clearly interpreted outside the local context. The WHO, therefore, has now established guidelines for influenza surveillance with a primary focus on the identification of episodes of severe acute respiratory infections (SARI) (WHO Global Influenza Programme, 2012). SARI surveillance aims to:

i. collect data on morbidity and mortality related to influenza-associated severe disease (resulting in hospital admissions)
ii. identify and understand the risk factors for severe disease
iii. provide a platform for undertaking disease burden estimation locally and assist in interpreting the results in a global context

Sentinel surveillance is a mechanism for systematically collecting data on a routine basis from a limited number of surveillance sites that are representative of the population under surveillance. Sentinel surveillance is a cost-effective and efficient way to collect high-quality epidemiological data in a timely manner. Influenza surveillance focuses on the two extreme presentations of the disease – ILI sentinel surveillance that monitors persons with milder forms of the disease seeking ambulatory care; and SARI sentinel surveillance that is aimed to identify persons with severe disease who have been admitted to hospital for treatment. When combined with laboratory confirmation for influenza, surveillance for both mild and severe disease contributes to understanding the complete spectrum of influenza illness including differences in the epidemiology of various types and subtypes of the influenza virus, risk factors for severe disease, and impact on healthcare delivery systems. The underlying population at risk (catchment population) can be estimated in the majority of the SARI sentinel sites. Thus, SARI sentinel surveillance is extremely useful for calculating incidence rates related to severe disease.

The WHO have established surveillance case definitions for ILI and SARI (Panel 1) (WHO Global Influenza Programme, 2012). The ILI case definition is generally intended for use in outpatient clinics while the SARI case definition is aimed at inpatient hospital settings. The SARI case definition aims to capture both influenza

related ALRI as well as influenza related exacerbations of chronic illnesses such as asthma or heart disease (the latter being more common in the elderly population than in children). Both case definitions require laboratory confirmation of the influenza virus in at least a proportion of the eligible cases (i.e. those satisfying the case definition). Since laboratory confirmation can only be conducted in a small proportion of ILI cases and catchment population cannot be estimated for most ILI sentinel sites, the WHO do not recommend using ILI sentinel surveillance for disease burden estimation. The sensitivity and specificity of the SARI case definition varies from 4.2 to 67% (median 55%) and 32 to 95% (median 65%) depending on the geographical location of the studies site (Mounts, personal communication). However, data from a proportion of studies that have stratified the sensitivity by age reveal that while the case definition is highly sensitive (range 70 to 96%) in children aged below five years, the sensitivity is lower in older children and adults (range 13 to 33%). On the other hand, the specificity of the case definition is poor in young children (range 4 to 22.5%), compared to older children and adults (range 80 to 86%). This means that SARI cases do not accurately reflect the true severe influenza disease burden in young children- the majority of the SARI cases are associated with other aetiologies.

However, when used in combination with a specific diagnostic assay like PCR, this case definition should capture the majority of the hospitalizations due to influenza-associated severe respiratory disease.

ILI- acute respiratory infection with:

- measured fever of ≥ 38°C
- and cough
- with onset within the last seven days

SARI– acute respiratory infection with:

- history of fever or measured fever of ≥ 38°C
- and cough
- with onset within the last seven days
- and requiring hospitalisation

Panel 1: Current WHO case definitions for influenza surveillance

While the revised WHO surveillance guidelines provide guidance to member countries on setting up SARI sentinel surveillance, with an aim to estimate disease burden associated with severe influenza, they do not provide methods for this purpose (WHO Global Influenza Programme, 2012). Methods / tools for estimating disease burden associated with severe influenza have been developed for the WHO as part of this doctoral thesis.

1.6. Evolution of this thesis

The body of work undertaken during the period of doctoral thesis needs to be viewed in three phases:

Preparatory work: The author led a study to estimate the disease burden due to RSV associated ALRI in young children (0-59 months) at global and regional level (blue boxes in Figure 4). Data from systematic review of published literature were supplemented with unpublished data collected through a consortium of researchers on childhood pneumonia and RSV; and primarily based in developing countries (RSV Study Group). The data were analysed, and summary estimates generated using meta-analysis. The methods for data collection and data analysis used in this thesis were thus piloted during this study.

Ph.D. thesis: The author primarily aimed to estimate the hospitalisations and mortality due to influenza associated ALRI in children aged 0-59 months (green boxes in Figure 4). In order to estimate hospitalisations indirectly from hospital-based studies not having a clear denominator population (at risk), the author estimated the number of hospital admissions due to severe ALRI in children aged 0-59 months to which the proportion of hospitalised ALRI cases positive for seasonal influenza would be applied (yellow boxes in Figure 4) Additionally, the author aimed to develop methods and tools for estimating influenza associated ALRI disease burden using SARI surveillance data (yellow boxes in Figure 4).

Additional outputs: The author estimated the hospital admissions and in-hospital deaths due to severe ALRI in children aged 0-59 months; and developed a manual

for the WHO to estimate disease burden associated with seasonal influenza (in all age groups) using SARI surveillance data (orange boxes in Figure 4).

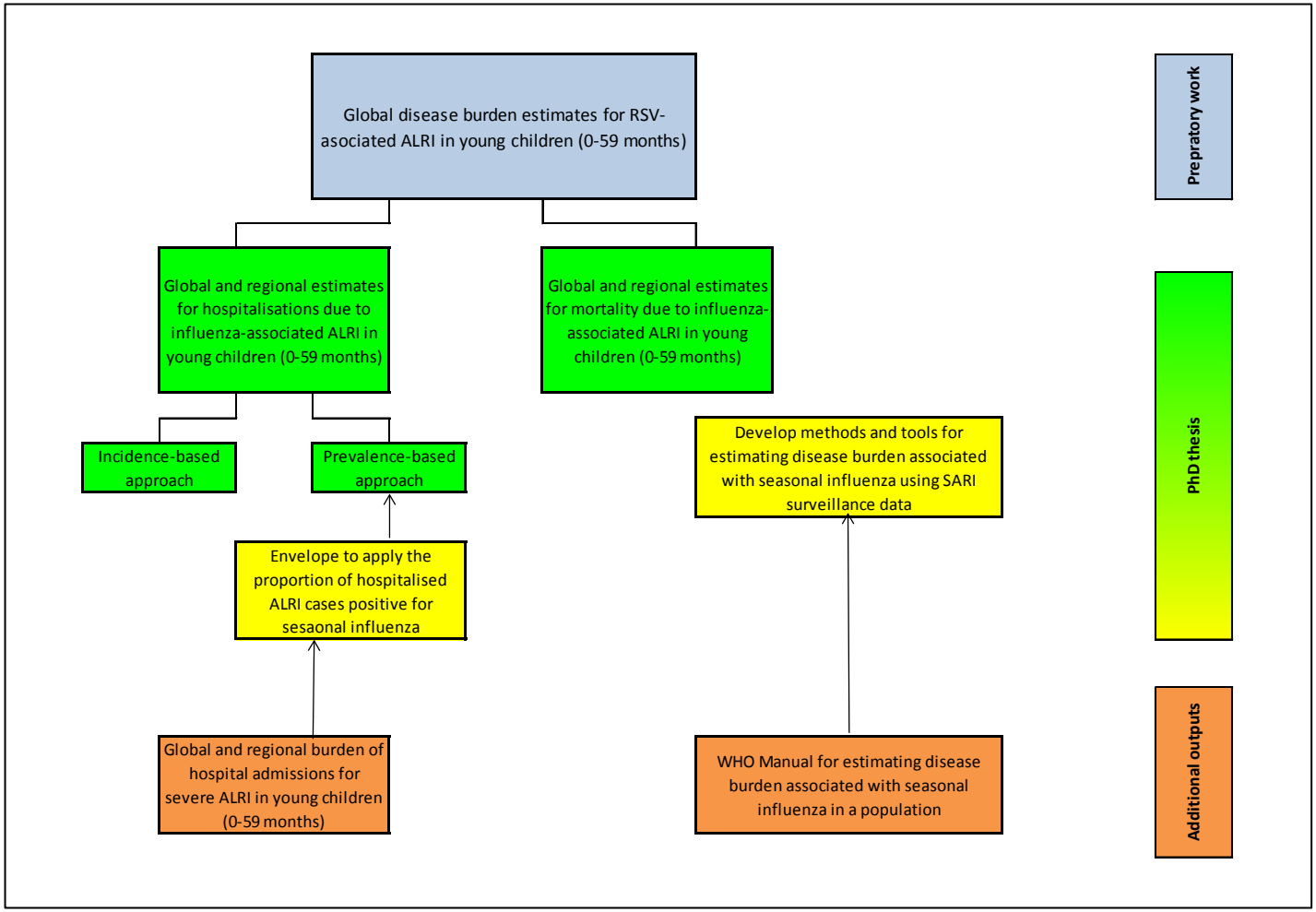

Figure 4: Flow diagram explaining the various components of this doctoral thesis

Chapter 2. Aims of the thesis

Acute lower respiratory infections are a leading cause of morbidity and mortality in young children all over the world. Though seasonal influenza is an important cause of ALRI, there are no global estimates of the burden of disease due to influenza-associated ALRI either in the paediatric or the adult age group. At the beginning of this thesis, there were only two systematic reviews of published literature on the burden of influenza-associated ALRI- one included 28 studies in children aged 0-19 years from all over the world (Bueving et al., 2005); and the other was based on 35 articles focussing only on 18 countries in East and South-East Asia and included all age groups (Simmerman and Uyeki, 2008). Both studies were unable to provide summary incidence rates either globally or for the region under study as data on incidence of influenza-associated ALRI were scarce. The 2009-10 influenza A(H1N1)pdm09 pandemic highlighted the need for baseline incidence and mortality data from seasonal influenza especially in the most vulnerable groups like young children. This thesis **primarily aims** to estimate the burden of disease due to influenza-associated ALRI resulting in hospitalisation in children aged less than 5 years for the year 2008 both globally and for the six WHO regions (please refer to section 1.6 and Figure 4 that illustrate how different components of this thesis are integrated as a unified body of work).

The **specific primary objectives** of are:

1. **Estimate the hospitalisations due to seasonal influenza-associated ALRI in young children, both globally and by WHO regions in the year 2008 using two different approaches-**

    a. an incidence-based approach using data from hospital-based studies having a clear denominator population (at risk)

    b. a prevalence-based approach using data from hospital-based studies NOT having a clear denominator population (at risk)

2. **Estimate the possible boundaries of seasonal influenza-associated ALRI mortality in young children, both globally and for industrialised and developing country regions in the year 2008 using two different approaches-**

    a. in-hospital case fatality ratio in influenza-associated ALRI to estimate deaths occurring in healthcare facilities

    b. identifying cause of death data in children not admitted to hospital (assigned by verbal autopsy) and concurrent influenza virus isolation in the same population to estimate influenza-associated ALRI deaths occurring outside healthcare facilities

As a **secondary aim**, this study aims to develop methods and tools for estimating disease burden associated with seasonal influenza using severe acute respiratory infections (SARI) surveillance in low and middle-income countries. The **specific secondary objectives** are:

i. Conduct a survey of end-users (primarily in low and middle income countries) to identify their needs so as to inform the design of the manual

ii. Develop specific methods and tools for estimating incidence, proportion of influenza positive cases and number of episodes of influenza-associated severe acute respiratory infections using data from SARI surveillance in low and middle income countries

Chapter 3. Burden of disease due to seasonal influenza-associated ALRI in young children

The guiding principle for the methodology underlying any disease burden estimation at global or national levels is that although perfect data sources will not be available for every country in every region, the systematic review process will identify available data that satisfy the quality criteria and are useful / valid for the generation of the best possible estimates. The study to estimate the burden of disease due to RSV-associated ALRI which was undertaken to pilot the methods for data collection and analysis used for this thesis (Nair et al., 2010), demonstrated that much of the aetiology-specific data on childhood pneumonia especially from the developing world remain unpublished (Appendix A8) . Hence, in addition to a systematic literature review, identifying and obtaining unpublished data especially from developing countries was one of the key activities for estimating the burden of disease due to seasonal influenza-associated ALRI using an incidence rate approach. Current Global Burden of Disease Estimates do not estimate / report hospitalizations associated with a disease (World Health Organization, 2008). Hospitalisations associated with a disease reflect the burden on hospital inpatient systems and are important while allocating resources and planning for augmenting hospital beds and associated facilities especially in resource constrained developing countries. In the absence of good quality mortality data (for deaths occurring in the community), in-hospital mortality indicates the likely lower bound of the overall mortality associated with the disease.

3.1. Hospitalisations due to seasonal influenza-associated ALRI

There are two sources of data to estimate hospitalisations due to seasonal influenza-associated ALRI- data from hospital-based studies having a defined denominator population at risk (incidence data); and data from hospital based studies where the underlying denominator population cannot be defined (proportion positive data).

3.1.1. Incidence-based approach

3.1.1.1. Methods

3.1.1.1.1. Literature search

A systematic literature review was conducted across the following electronic databases – Medline (Ovid), Embase, CINAHL, Global Health, Web of Science, WHOLIS, LILACS, and IndMed. Additionally, a Chinese language database (The China National Knowledge Infrastructure or CNKI (www.global.cnki.net), was searched for studies (with a clear denominator of the population at risk) published in Chinese language during the same period. A grey literature database (SIGLE) was also searched. The detailed search strategy is placed in the appendix (Appendix A3). The search was limited to studies published between 1 January, 1995, and 31 October, 2010 for the following reasons:

- since the estimates are being generated for the year 2008, data from studies published prior to 1995 were considered to be dated.
- most of the studies published prior to 1995 used serologic diagnosis which had poor sensitivity and specificity thus making it difficult to combine their results with more advanced techniques used in the past decade.

In order to conform to the PRISMA guidelines for systematic reviews and meta-analysis, another researcher (Valerie Evans, MSc) independently performed the literature search and data extraction. The literature search and data abstraction for Chinese language articles were conducted by another researcher (Jian Shayne F. Zhang, MPH) who read Chinese as a first language and had access to these databases. All identified studies were assessed using the eligibility criteria detailed in Panel 2. No language or publication restrictions were applied. Data were extracted onto a data extraction template designed on Microsoft Excel (Microsoft Office 2003). Any disagreements were discussed and arbitrated by the supervisor for this doctoral thesis (Prof. Harry Campbell).

Inclusion criteria

- Studies with data on children with laboratory confirmed influenza and hospitalised for ALRI
- Studies published between 1 January 1995 and 31 October 2010
- Studies should have been carried out for a minimum of one year (except in temperate regions where influenza seasonality is more clearly defined and for studies reporting case fatality ratio). This is important as influenza is a seasonal disease
- Studies in children less than 5 years of age, or should have reported data for this age group separately
- Studies reporting influenza incidence or mortality for a minimum of the first year of life

Exclusion criteria

- Studies where influenza was studied as a co-infection rather than a primary outcome
- Case definition was not clearly defined and / or not consistently applied
- Case ascertainment was conducted only during an epidemic period
- Study data after 21 April, 2009 (onset of influenza A(H1N1)pdm09 pandemic
- Incidence and mortality were estimated using modelling techniques

Panel 2: Eligibility criteria for selection of studies reporting incidence of hospitalised influenza-associated ALRI in young children

3.1.1.1.2. Unpublished data

Thirteen leading researchers on paediatric influenza and pneumonia were identified through their publication track record as well as through extensive consultations with subject experts- primarily those involved in the RSV-associated ALRI disease burden estimation project. This led to the formation of an international consortium ("Influenza Study Group") that consisted primarily of researchers working in developing countries. The author organised and led a two-day meeting of the Influenza Study Group in Edinburgh, UK on February 3-4, 2010. This meeting was funded by the World Health Organisation's Global Influenza Programme.

During the two-day meeting, the Influenza Study Group discussed extensively the availability of data (with a clear denominator on the population at risk) on paediatric influenza in children aged below five years and finalised common case definitions for analysing all available data. The group agreed to either re-analyse their already published data or share hitherto unpublished data from on-going studies on a common data extraction template designed in Microsoft Excel (Microsoft Office 2003). The group suggested the inclusion of some other research groups who, to the best of their knowledge, had conducted similar studies but were not invited to the meeting. These groups were contacted and enlisted into the Influenza Study Group. Finally, fifteen research sites from 12 countries contributed unpublished data for estimating incidence of hospitalised influenza-associated ALRI in children aged 0-59 months.

3.1.1.1.3. Case definitions

Though influenza causes a wide range of illness including (ranging from mild influenza like illness to more severe disease and sequelae) (Figure 3), the Influenza Study Group agreed that there was a need to limit this exercise to estimation of incidence and case fatality related to influenza-associated ALRI in young children (due to paucity of data on mild illness and sequelae and costs associated with influenza disease). Since the majority of published and unpublished data were for influenza-associated ALRI resulting in hospitalisation, and hospitalised cases are reflective of disease severity and the overall burden on the healthcare system, this

thesis focuses only on incidence and case fatality related to hospitalised influenza-associated ALRI.

Most investigators used modified versions of the case definitions for clinical pneumonia, severe pneumonia, and influenza surveillance that were established by WHO under the Integrated Management of Childhood Illness (IMCI) programme or the US Centres for Disease Control and Prevention (US CDC's) Influenza Surveillance Programme (Department of Child and Adolescent Health, 2005, Ortiz et al., 2009). The group agreed to use the term ALRI rather than pneumonia because a proportion of children with lower respiratory complications of influenza might not only present with pneumonia but also with bronchiolitis. Hospitalised influenza-associated ALRI is defined as identification of influenza virus (using valid diagnostic tests) in a child with either cough or difficulty in breathing and hospitalised for a respiratory ailment.

3.1.1.1.4. Ethical approval

The author conducted a Self-Audit for Level 1 Ethical Review in relation to this project. This was done using a checklist developed by the School of Health in Social Science and adopted by the Post Graduate Ethics Committee of the College of Medicine and Veterinary Medicine, University of Edinburgh. Since no foreseeable ethical risks were identified (as all analysis were on secondary data), a formal ethical approval was not required. The individual collaborating sites re-analysing primary data sought ethical approvals from their respective Institutional Review Boards. A copy of the Self-Audit Checklist for Level 1 is placed in the Appendix A1.

3.1.1.1.5. Statistical analysis

3.1.1.1.5.1. Data imputation

While twenty six and thirty three of the 39 included studies reported incidence estimates for infants (aged 0-11 months), and young children (0-59 months) respectively, only 24 studies reported incidence rates for both 0-11 months as well as 0-59 months. For the remaining fifteen studies -10 published (Sutmoller et al., 1995, Henrickson et al., 2004, Poehling et al., 2006, Coffin et al., 2007, Grijalva et al., 2006, Grijalva et al., 2007b, Rojo et al., 2006, Forster et al., 2004, Ajayi-Obe et al.,

2008, Hasan et al., 2006) and 5 unpublished (Bhat and colleagues, unpublished; Gordon and colleagues, unpublished; Lindblade and colleagues, unpublished ; Clara and colleagues, unpublished ; Lucero and colleagues, unpublished), data imputation was employed using the median incidence rate ratio (IRR) as has been employed previously by Rudan and Nair (Rudan et al., 2004, Nair et al., 2010). Using incidence rate data from the 24 studies reporting incidence rates for the age groups 0-11 months and 0-59 months, the median incidence rate ratio (IRR) for children in the age group 0-23 months and 0-59 months was calculated. Relative to an incidence rate of 1.0 in the age group 0-11 months, the median IRR for the age group 0-23 months and 0-59 months was calculated to be 0.96 and 0.53 respectively. This median IRR was then applied to the reported incidence rates of hospitalised influenza-associated ALRI for 0-11 months, or 0-23 months or 0-59 months to estimate the incidence rate for the missing age groups. In order to assess the validity of data after imputation, a sensitivity analysis was carried out by including only those studies which had data for the full age range (0-59 months) (for results see Table 25).

3.1.1.1.5.2. Adjustments and assumptions

The following statistical adjustments/assumptions were made for data synthesis:

- If the duration of the study was not in exact multiples of one year (e.g. 18 months, 30 months etc.), the annualised incidence rate was calculated and reported by adjusting for the population at risk.
- If clinical specimens were collected in only a proportion of eligible cases (using a systematic method) and data on all eligible cases were available, the incidence rate was adjusted by scaling for the proportion sampled.

3.1.1.1.5.3. Meta-analysis

A meta-analysis of the data (through April 15, 2009) from studies reporting incidence of hospitalised influenza- associated ALRI was conducted (using Stata 11.2) and the pooled estimates along with 95% CIs have been reported. The random effects model (DerSimonian-Laird method) was used since heterogeneity in the data was anticipated (DerSimonian and Laird, 1986). The random effects model accounts for both in study and between study heterogeneity (Riley et al., 2011). This decision

is statistically valid since in the absence of significant heterogeneity ($p<0.05$), the meta-estimates (and 95% CI) from the random and fixed effects models are identical. The incidence rates were estimated globally and by regions- for industrialised and developing countries as well as for the six WHO regions.

3.1.1.1.5.4. Number of hospitalised influenza-associated ALRI cases in 2008

The incidence meta-estimates for hospitalised influenza-associated ALRI were applied to the population of children younger than 5 years in 2008 both globally as well as in the six WHO regions to estimate the number of new episodes of influenza-associated hospitalised ALRI in 2008. Countries were designated as industrialised or developing on the basis of UNICEF's classification (United Nations Children's Fund, 2012). The child population estimates for 2008 are as in the UN Population Division's database, "World Population Prospects: The 2010 revision" (http://esa.un.org/unpd/wpp/unpp/panel_population.htm).

3.1.1.2. Results

Thirty-nine hospital-based studies (24 published and 15 unpublished) using passive case ascertainment (i.e. a child with ALRI being brought to a health facility) and satisfying the eligibility criteria were identified (Figure 5). Eight studies were in rural populations, 15 in urban and the remainder involved a mixture of rural and urban populations (Table 4). Fifteen studies were either cohort studies or were nested in a demographic surveillance site and were thus able to report the denominator population at risk; four studies were able to identify the catchment population for the hospital and adjust for the proportion of total population seeking care at the given hospital a using healthcare utilisation survey (Azziz-Baumgartner et al., 2012, Feikin et al., 2011, Jordan et al., 2009); and 20 studies reported the catchment population based on a census-derived denominator. No additional studies were identified from the search in Chinese language databases.

Twenty one of the 39 included studies were from developing countries. Sixty two percent (13/21) of the studies from developing countries were unpublished (Figure 6). By contrast, unpublished studies contributed only 11 percent (2/18 studies) of the

data from industrialised countries. There were no data from the Eastern Mediterranean Region. One study in native American Indian population (Bhat and colleagues, unpublished) was included in the meta-estimates for developing countries as the socio-economic and demographic risk factors for ALRI in these populations are similar to those in the developing countries. The data from both the developing as well as industrialised countries were significantly heterogeneous ($p<0.0005$, I^2 >80 percent).

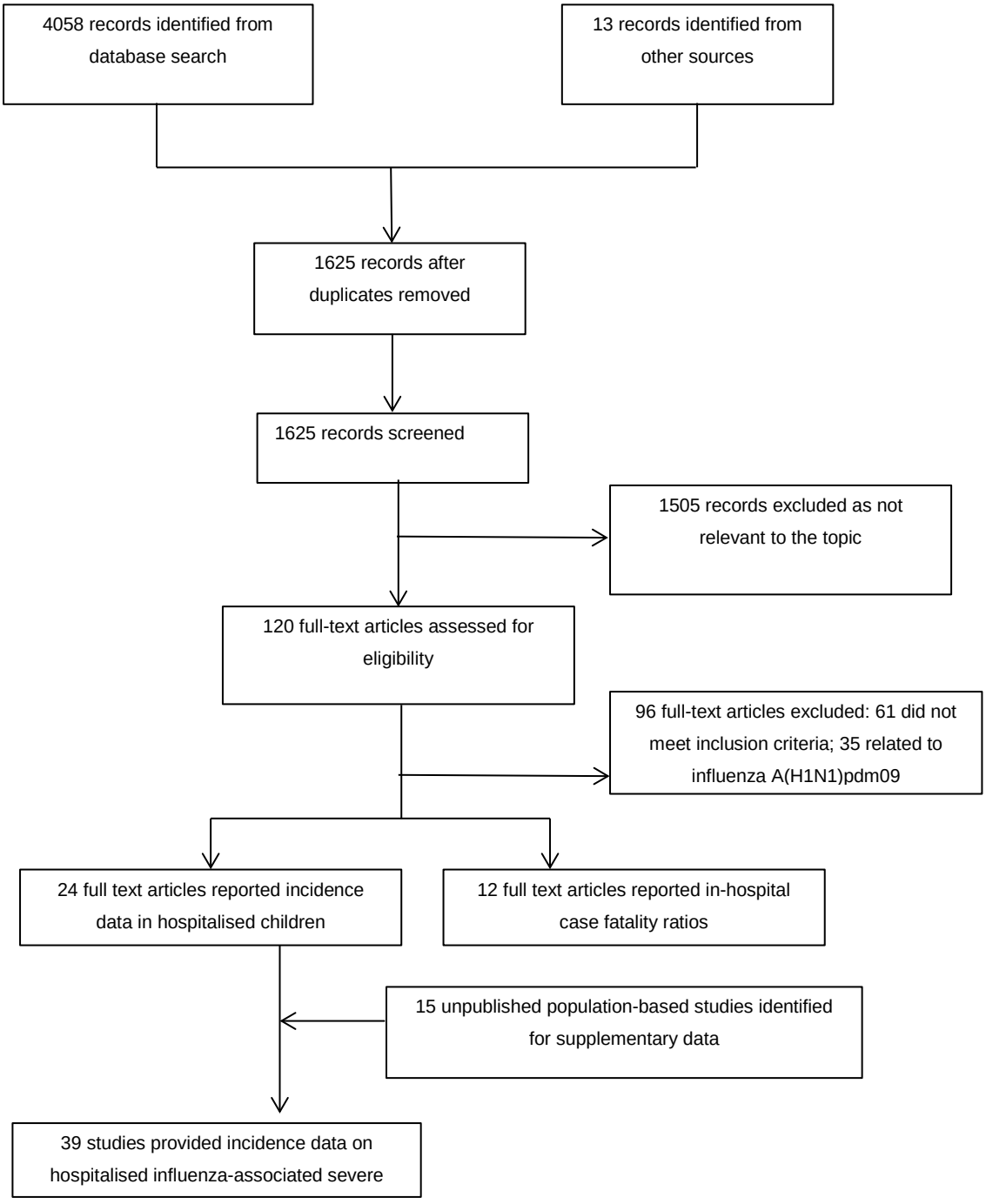

Figure 5: Flow diagram for selection of studies reporting incidence of hospitalised influenza-associated ALRI in young children

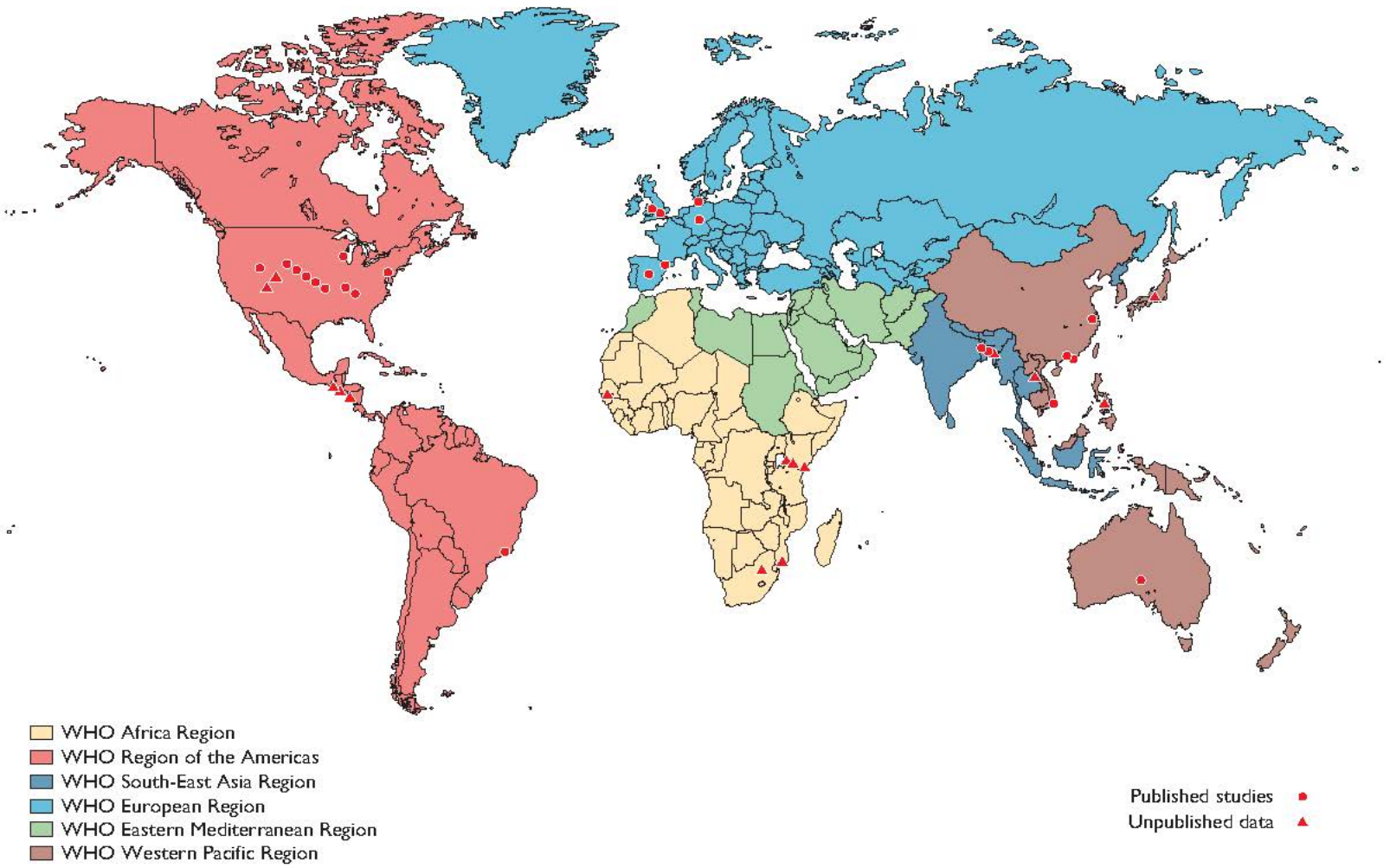

Figure 6: Location of the 39 studies reporting incidence of hospitalised influenza-associated ALRI in young children by World Health Organization Regions

Table 4: Incidence estimates of influenza-associated ALRI in hospitalised children younger than 5 years from published and unpublished studies by World Health Organization Regions

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
Africa							
Soweto, South Africa; urban (Madhi and colleagues, unpublished) †	1998-2004	Defined population base (n=39876)	Hospitalised ALRI cases with lower respiratory tract infection diagnosed by a physician	Nasopharyngeal aspirate. DFA	2.6	2.1	0.9
Manhiça district, Mozambique; rural (Roca and colleagues, unpublished)	2006-2007	Defined population base (n= 3291 cyo)	Children admitted to hospital with cough and difficulty breathing and chest wall indrawing	Nasopharyngeal aspirate. Multiplex RT-PCR	3.5	3.3	1.6
Kilifi district, Kenya; rural (Berkley and colleagues, unpublished)	2007	Defined population base (n=44544)	Children admitted to hospital with history of cough or difficulty breathing AND one or more of the following: lower chest wall indrawing, hypoxia, inability to drink or breastfeed, impaired consciousness	Nasal wash. Multiplex real-time PCR	3	2.5	1.1
Bondo district, Kenya; rural (Ope and colleagues,	2007-2009	Census-derived estimate	A child hospitalized with cough or difficulty breathing, plus at least one of the following signs:	Nasopharyngeal and / or oropharyngeal wash. Real-time RT-PCR	1.3	1.6	1.0

cyo=child years observed; DFA= Direct immunofluorescence ; RT-PCR=Reverse Transcriptase Polymerase Chain Reaction; PCR=Polymerase Chain Reaction

* Data in parentheses are computed incidence estimates from data imputation

† Excluded neonates (0-27 days)

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
unpublished)†		(n=55117)	• lower chest wall indrawing • nasal flaring				
The Greater Banjul area and Upper River Region, The Gambia; periurban and rural (Howie and colleagues, unpublished) ‡	2007-2008	Defined population base (n=24378)	A child hospitalized with cough or difficulty breathing AND either inability to drink or breastfeed or lethargic or unconscious or vomits everything or had history of convulsions, or chest wall indrawing or stridor in a calm child	Nasopharyngeal aspirate. Mass Tag PCR	0	0.6	0.4
Lwak, Kisumu, Kenya; rural (Katz and colleagues, unpublished)	2008	Census-derived estimate (n=3825 cyo)	A child hospitalized with elevated respiratory rate for age using IMCI cut-offs (for pneumonia) or maternal report of convulsions, inability to drink or breastfeed, or vomiting everything, or on examination has lethargy, unconsciousness, lower chest wall indrawing, stridor, or an oxygen saturation < 90%	Nasopharyngeal and oropharyngeal swabs. Real-time RT-PCR	1.3	0.6	0.8
Americas							
Nashville (TN), USA; urban (Neuzil et al., 2002)	1974 - 1999	Defined population base (n=3041 cyo)	Hospitalised ALRI	Nasal wash. Viral culture	3.4	3.5	2.3

IFA= Indirect immunofluorescence

‡ Included children aged 2-59 months

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
Rio de Janeiro, Brazil; urban (Sutmoller et al., 1995)	1987-1989	Defined population base (n=262)	Hospitalised ALRI: tachypnoea, chest retractions, wheezing, rales, stridor or cyanosis	Nasopharyngeal aspirate. IFA, viral culture	(4.8)	(4.5)	2.5
Milwaukee (WI), USA; mixed urban-rural (Henrickson et al., 2004)	1996-1998	Census-derived estimate	Hospitalised ALRI	Nasopharyngeal swabs, bronchoalveolar lavage, throat swabs, endotracheal aspirates. Multiplex PCR, tissue culture, EIA	(2.8)	(2.6)	1.5
Monroe County (NY) and Davidson County (TN), USA; urban (Iwane et al., 2004)	2000-2001	Defined population base	Hospitalised ALRI	Nasal swab and throat swab. Viral culture and RT-PCR	1.7	1.2	0.6
Nashville, Rochester (NY) and Cincinnati (OH), USA; urban (Poehling et al., 2006)	2000-2004	Defined population base	Hospitalised ALRI	Nasal swab and throat swab. Viral culture and RT-PCR	(1.7)	(1.7)	0.9
Philadelphia (PA), USA; urban (Coffin et al., 2007) §	2000-2004	Census-derived estimate (n=87216)	Hospitalised ALRI (Discharge diagnosis ICD-9 codes: 487, 487.0, 487.1, 487.8 and / or lab reports)	Nasal aspirate. Solid-phase immunoassay, DFA and viral culture	(4.2)	4.2	2.1
Colorado (CO), USA; mixed urban-rural (Simões and colleagues, unpublished)§	2000-2008	Census-derived estimate (n=334810)	Hospitalised ALRI (Discharge diagnosis ICD-9 codes: 487.0, 487.1, 487.8, 487.9, 488.0, 488.1)	Nasal wash. Viral culture, EIA, RT-PCR	3.9	3.0	0.8

EIA= Enzyme-linked immunoassay

§ Incidence estimated with hospital discharge records and laboratory data

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
Salt Lake county (UT), USA; mixed urban-rural (Ampofo et al., 2006)[§]	2001-2004	Census-derived estimate (n=71784)	Hospitalised ALRI (Discharge diagnosis ICD-9 codes that met consensus for ILI)	Nasopharyngeal aspirate. DFA	1.8	1.9	0.9
Davidson County (TN), USA; mixed urban-rural (Grijalva et al., 2006)	2003-2004	Census-derived estimate (n=37813)	Hospitalised ALRI	Nasal and throat swabs. Viral culture, RT-PCR, rapid tests, IFA, serology	(4.6)	4.5	2.4
Multistate, USA; mixed urban-rural (Schrag et al., 2006)[§] [**]	2003-2004	Census-derived estimate (n=1164869)	Hospitalised ALRI (Discharge diagnosis ICD-9 codes: 038.8, 038.9, 345.1, 461.0, 464.0, 464.1, 464.10, 464.11, 464.2, 464.20, 464.21, 464.4, 465.0, 466.0, 466.1, 478.9, 480.0-486.0, 487.0, 493.0, 779.0, 780.3, 780.6)	Viral culture, DFA, IFA, rapid antigen test, RT-PCR	2.2	1.6	0.9
Navajo and WMA reservations, USA; rural (Bhat and colleagues, unpublished)	2003-2005	Defined population base (n=857)	Physician diagnosed hospitalised ALRI	Nasopharyngeal aspirate. Viral culture and serology	(3.1)	(3.0)	(1.6)
Davidson County (TN), Monroe County (NY) and Hamiltion County (OH), USA; mixed urban-rural (Grijalva et al., 2007b)	2004-2005	Census-derived estimate (n=141338)	Hospitalised ALRI	Nasal and throat swabs. Viral culture, RT-PCR, rapid tests, IFA, serology	(3.5)	3.4	1.8

[**] Detailed age-specific incidence estimates obtained directly from authors

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
Multistate, USA; mixed urban-rural (Dawood et al., 2010)**	2004-2008	Census-derived estimate (n=5633069)	Influenza-associated pneumonia: any hospitalized child with laboratory-confirmed influenza who had evidence of a new pneumonia on at least 1 chest radiograph obtained during the current admission or hospitalization	Nasopharyngeal and oropharyngeal swabs. Viral culture, DFA, IFA, rapid antigen test, RT-PCR	0.9	0.6	0.4
Managua, Nicaragua; urban (Gordon and colleagues, unpublished) ††	2007-2008	Defined population base (n=1024)	Hospitalised child with cough and indrawing of chest wall	Nasal and throat swabs. RT-PCR	(4.2)	(4.1)	(3.2)
Santa Rosa, Guatemala; mixed rural and small towns (Lindblade and colleagues, unpublished)	2008	Census-derived estimate (n=34465)	Hospitalized pneumonia and evidence of acute infection [fever >38°C, hypothermia (temp <35.5° C), abnormal WBC (count <5500 or >15000 per cu. mm. or abnormal WBC differential) and at least one sign/symptom of respiratory disease (tachypnea, cough, sputum production, pleuritic chest pain, hemoptysis, difficulty breathing, shortness of breath, sore throat; in children <2 years old only: not eating, drinking or breastfeeding, child pauses repeatedly	Nasopharyngeal and oropharyngeal swabs. Real-time RT-PCR	(1.2)	(1.1)	0.6
Santa Ana, El Salvador, mixed urban-rural (Clara and colleagues, unpublished)	2008	Census-derived estimate (n=21827 cyo)	Hospitalized with cough or difficulty breathing and at least one danger sign (i.e. chest wall indrawing, stridor while calm, convulsions, inability to drink, lethargy,	Nasal and oropharyngeal swabs. Real-time RT-PCR	(3.2)	(3.1)	1.7

†† Included children aged 2 years up to 5 years

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
			unconsciousness or intractable vomiting)				
Europe							
Kiel, Germany; urban (Weigl et al., 2005a)	1996-2000	Census-derived estimate	Hospitalisation for ALRI (Discharge diagnosis ICD 9 codes: 460 to 490; and J00 to J22 in ICD-10)	Nasopharyngeal aspirate. RT-PCR	1.5	(1.4)	1.2
Madrid, Spain; urban (Rojo et al., 2006)	1997-2003	Census-derived estimate (n=149602)	Hospitalisation for ALRI (presence of respiratory symptoms and signs along with infiltrates on chest X-ray)	Nasal or throat aspirate. Viral culture and subsequent fluorescent staining with monoclonal antibodies	(1.1)	(1.0)	(0.6)
Multicentre, Germany; mixed rural-urban (Forster et al., 2004)**	1999-2001	Census-derived estimate	ARI requiring hospitalisation	Nasopharyngeal aspirate. PCR	1.8	1.6	(0.9)
Leicester, United Kingdom; mixed urban- rural (Nicholson et al., 2006)	2001-2002	NHS database (n=56395)	ARI requiring hospitalisation	Nasal and throat swabs. PCR	2.4	2.2	1.6
Gipuzoka, Spain; mixed urban-rural (Montes et al., 2005)	2001-2004	Census-derived estimate	ARI requiring hospitalisation	Nasopharyngeal aspirate. Viral culture and RT-PCR	2.5	1.6	0.9
East London, United Kingdom; urban (Ajayi-Obe et al., 2008)	2002-2004	Census-derived estimate (n=15177)	ARI requiring hospitalisation	Nasopharyngeal aspirate. IFA and PCR	(2.9)	2.8	1.6
South East Asia							

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
Mirzapur, Bangladesh; rural (Hasan et al., 2006)	1993-1996	Defined population base (n=252)	ALRI requiring hospitalisation: h/o fever, cough, difficulty in breathing (respiratory rate >50 breaths / min in children aged 0-11 months and >40 breaths / min in children aged 12-59 months), wheezing, chest wall indrawing	Nasopharyngeal aspirate. EIA	(2.0)	2.0	(1.1)
Kamalapur, Bangladesh; urban (Brooks et al., 2010) ‡‡	2004-2007	Defined population base (n=5000)	Hospitalised pneumonia with chest wall indrawing	Nasopharyngeal wash. Viral culture	0.8	1.1	0.6
Sa Kaeo and Nakhon Phanom, Thailand; rural (Simmerman and colleagues, unpublished)	2005-2008	Census-derived estimate (n=83200)	Hospitalisation with evidence of acute infection (reported fever or documented temperature >38.2º C within 24 hours of admission, or reported chills or documented temperature of <35.5º C within 24 hours of admission, or abnormal white blood cell count (WBC>11,000/mm^3 or WBC<3,000/mm^3) or abnormal differential) with signs (abnormal breath sounds or tachypnea) or symptoms (cough, sputum production, hemoptysis, chest pain, dyspnea, or rhinitis) of respiratory tract disease	Nasopharyngeal swabs. RT-PCR and viral culture	6.0	7.2	5.3
Kamalapur, Bangladesh; urban (Brooks and colleagues, unpublished)‡‡	2008	Defined population base (n=5710)	Hospitalised ALRI with chest wall indrawing with or without WHO specified danger signs	Nasopharyngeal wash. RT-PCR and tissue culture	1.8	2.1	1.0

‡‡ All eligible subjects were followed up weekly at home by trained Field Research Assistants (FRAs) who referred children with findings suggestive of respiratory disease to the clinic

Location; population characteristic; study period (reference)	Study period	Study population (number)	Case definition	Specimen and Diagnostic test(s)	Incidence of influenza-associated hospitalised ALRI (per 1000 children per year) *		
					0-11 months	0-23 months	0-59 months
Western Pacific							
South Australia, Australia; mixed rural-urban (D'Onise and Raupach, 2008)§	1996-2006	Census-derived estimate	Hospitalised ALRI (Discharge diagnosis ICD-10 codes J-10 and J-11)	Details of specimen not available. Viral culture, PCR	1.5	(1.5)	0.6
Hong Kong SAR, China; urban (Nelson et al., 2007)§	1997-1999	Census-derived estimate (n=324538)	Hospitalised ALRI	Nasopharyngeal aspirate. IF followed by viral culture and serology	4.8	4.6	3.0
Bohol, Philippines; mixed urban-rural (Lucero and colleagues, unpublished)†	2000-2004	Defined population base (n=20516 cyo)	Hospitalised ALRI (cough, difficulty breathing with chest indrawing or WHO specified danger signs)	Nasopharyngeal aspirate. Viral culture and PCR	2.4	2.0	(1.3)
Soma, Japan; urban (Sato and colleagues, unpublished)	2002-2008	Defined population base (n=5692)	Hospitalised ALRI based on physician diagnosis	Nasal swab. Immunochromatography	5.6	6.0	4.8
Hong Kong SAR, China; urban; (Chiu et al., 2009)	2003-2006	Census-derived estimate	Hospitalised ALRI	Nasopharyngeal aspirate. DFA and viral culture	7.4	7.3	7.2
Nha Trang, Vietnam; urban (Yoshida et al., 2010)	2007-2008	Census-derived estimate (n=13952)	Hospitalised ALRI	Nasopharyngeal aspirate. PCR	16.9	17.7	8.7
Suzhou district, China; mixed urban-rural (Ji et al., 2010)§	2007-2008	Census-derived estimate (n=481470)	Hospitalised ALRI based on physician diagnosis	Nasopharyngeal aspirate. DFA	0.6	0.4	0.3

Overall, the incidence rates were highest in infants (aged 0-11 months). The incidence in infants (aged 0-11 months) was about 2.5 to 3 times that in children aged 12-59 months (Figure 7). Thirteen studies (seven in developing and six in industrialised countries) reported the detailed incidence in the first year of life. Although in general the incidence was highest in the first five months of life, this difference was more marked in the studies from industrialised countries (Figure 8, Figure 9).

There were marked regional variations in the incidence of influenza-associated hospitalised ALRI in both infants (0-11 months) as well as young children (0-59 months). Globally in both groups, incidence rates were highest in the Western Pacific Region of the WHO. At any given site, the incidence of influenza-associated hospitalised ALRI varied widely from year to year (sometimes by as much as two magnitudes) - depending on the type and sub-type of circulating influenza virus (Table 5). Data on incidence of influenza-associated ALRI by type and sub-type were scarce. Such data were available only from three sites (Bondo, Kenya; Bohol, Philippines; and Hong Kong). Data from all three sites indicate that influenza A conferred 64-100% of the disease burden due to seasonal influenza-associated hospitalised ALRI in young children.

The overall incidence of influenza-associated hospitalised ALRI was 1.5 (95% CI 1.0 to 2.3) episodes per 1000 children per year in developing countries compared to 1.2 (95% CI 0.9 to 1.6) episodes per 1000 children per year in industrialised countries (Figure 10). Thus, it is estimated that in the year 2008, about 911,000 (95% CI 617,000 to 1.4 million) new episodes of influenza-associated severe disease resulted in hospitalisations worldwide in children younger than 5 years (Table 6). The burden was disproportionately higher in infants (0-11 months) - they contributed to over 40 percent of the overall burden in young children. As expected, only seven percent of the overall cases globally occurred in industrialised countries (where 10 percent of the global under-5 population reside).

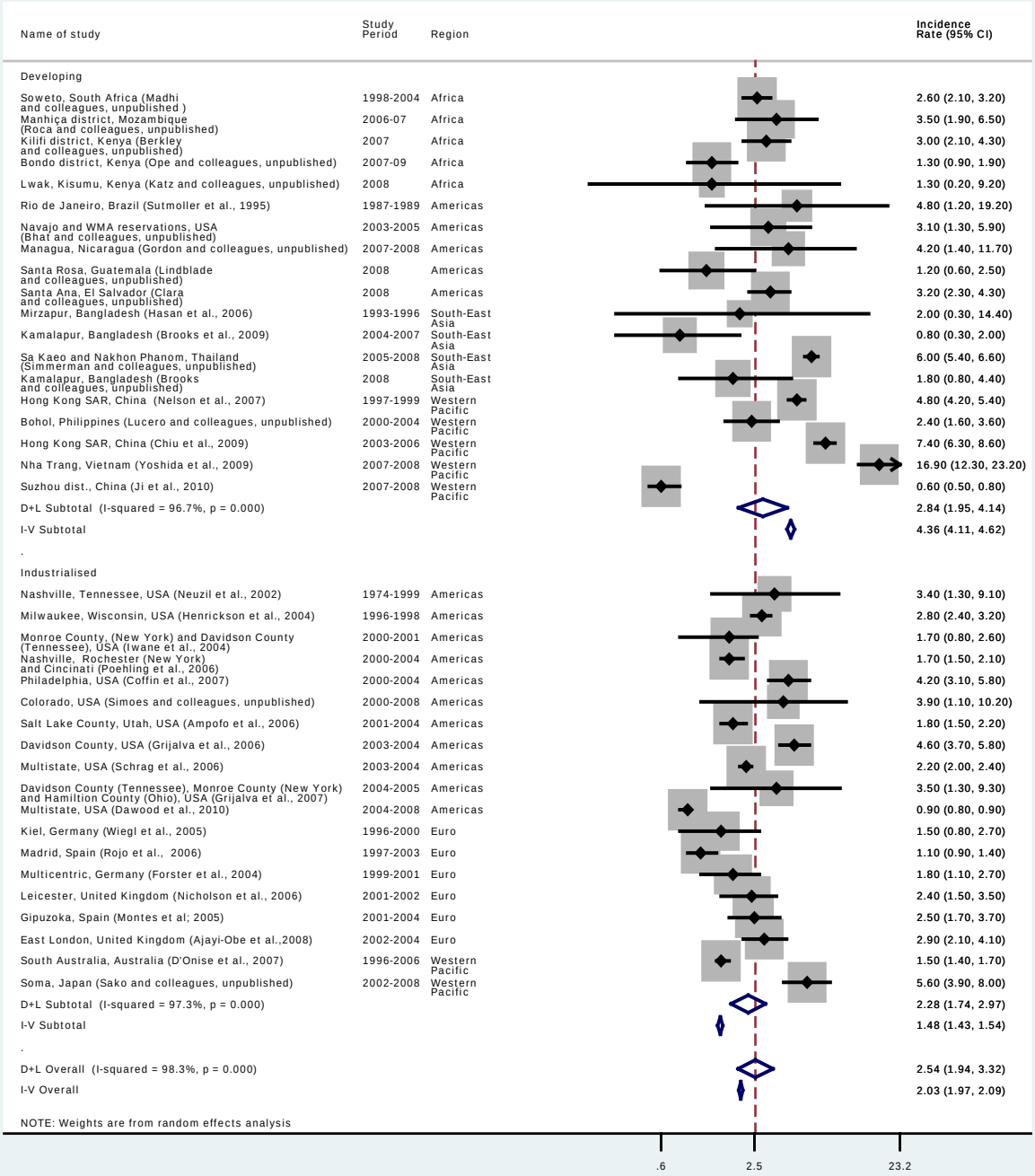

Figure 7: Forest plot of incidence estimates of influenza-associated hospitalised ALRI in children aged 0-11 months

D+L (overall) indicates meta-estimate by random effects analysis

I-V (overall) indicates meta-estimate by fixed effects analysis

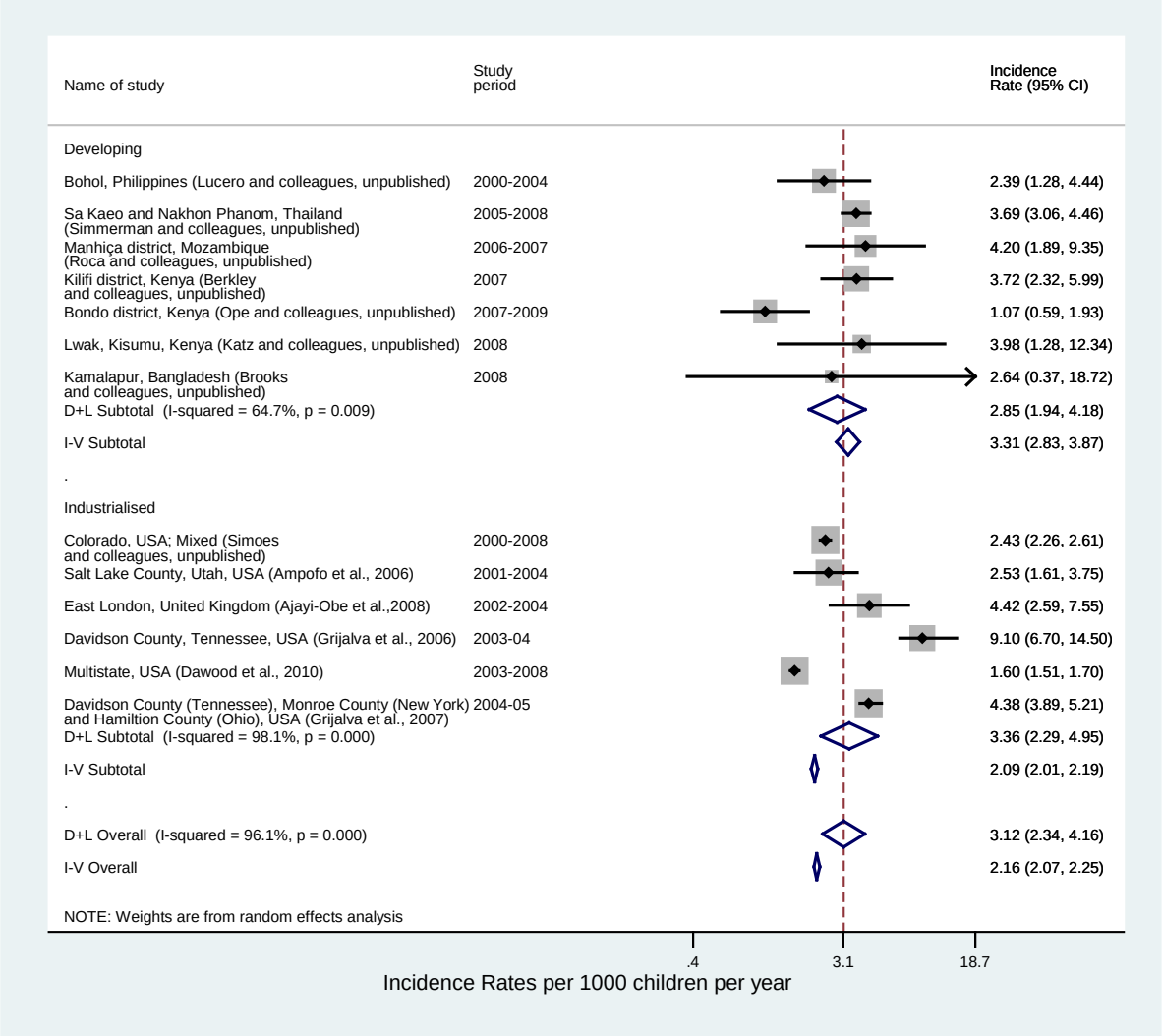

Figure 8: Forest plot of incidence estimates of influenza-associated hospitalised ALRI in children aged 0-5 months

D+L (overall) indicates meta-estimate by random effects analysis

I-V (overall) indicates meta-estimate by fixed effects analysis

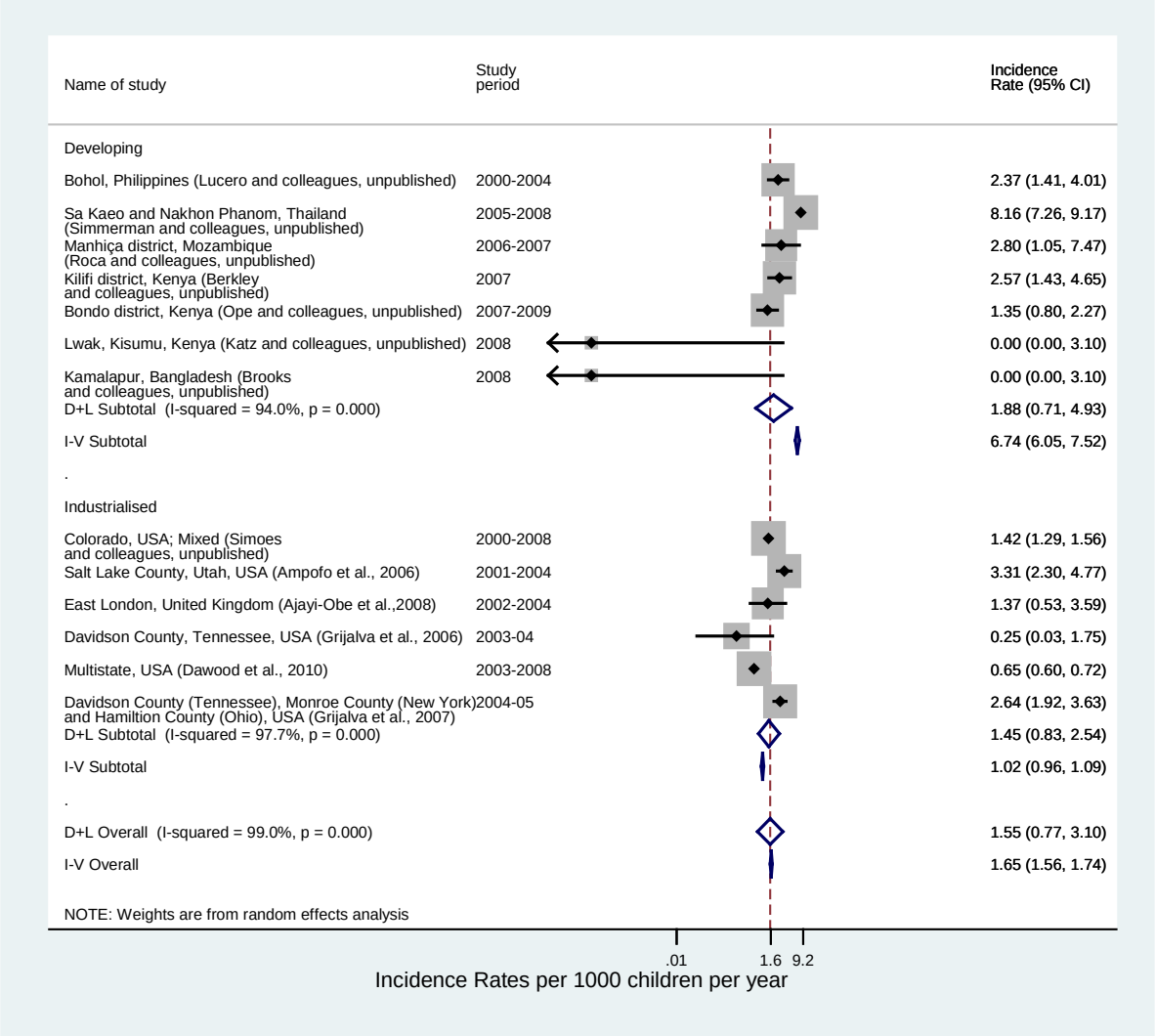

Figure 9: Forest plot of incidence estimates of influenza-associated hospitalised ALRI in children aged 6-11 months

D+L (overall) indicates meta-estimate by random effects analysis

I-V (overall) indicates meta-estimate by fixed effects analysis

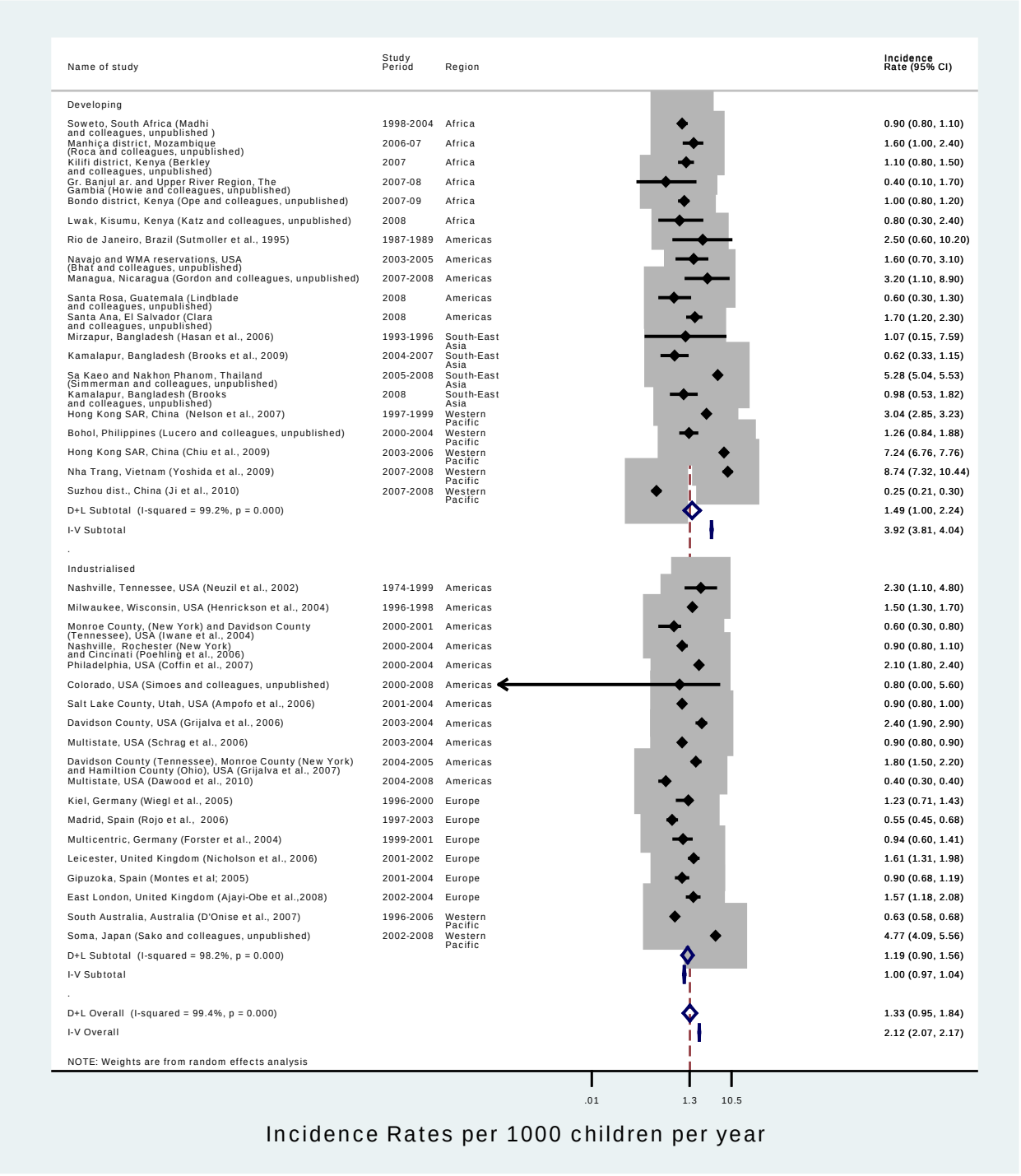

Figure 10: Forest plot of incidence estimates of influenza-associated hospitalised ALRI in children aged 0-59 months

D+L (overall) indicates meta-estimate by random effects analysis

I-V (overall) indicates meta-estimate by fixed effects analysis

Table 5: Annual variation in the incidence of influenza-associated hospitalised ALRI in children younger than 5 years by type and sub-type of circulating virus, by World Health Organization Regions

Location; (reference)	Study period	Incidence of influenza A(H1N1 & H3N2)-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza B-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza (all types and sub-types)-associated hospitalised ALRI (per 1000 children per year)		
		Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months
Africa										
Bondo district, Kenya (Ope and colleagues, unpublished)	2007-2008	0.8	1.4	1.0	0	0	0	0.8	1.4	1.0
	2008-2009	1.6	1.7	1.0	0.2	0.2	0.2	1.8	1.9	1.2
Americas										
Nashville, Rochester (NY) and Cincinnati (OH), USA (Poehling et al., 2006)	2000-2001	NA	NA	NA	NA	NA	NA	NA	NA	0.6
	2001-2002	NA	NA	NA	NA	NA	NA	NA	NA	0.9

Location; (reference)	Study period	Incidence of influenza A(H1N1 & H3N2)-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza B-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza (all types and sub-types)-associated hospitalised ALRI (per 1000 children per year)		
		Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months
	2002-2003	NA	NA	NA	NA	NA	NA	NA	NA	0.4
	2003-2004	NA	NA	NA	NA	NA	NA	NA	NA	1.5
Colorado (CO), USA (Simoes and colleagues, unpublished)	2000	NA	NA	NA	NA	NA	NA	0.8	0.5	0.1
	2001	NA	NA	NA	NA	NA	NA	2.2	1.6	0.4
	2002	NA	NA	NA	NA	NA	NA	2.4	2.2	0.7
	2003	NA	NA	NA	NA	NA	NA	12.1	10	2.7
	2004	NA	NA	NA	NA	NA	NA	1.1	0.7	0.2
	2005	NA	NA	NA	NA	NA	NA	4.1	2.9	0.8
	2006	NA	NA	NA	NA	NA	NA	4.8	3.6	0.9
	2007	NA	NA	NA	NA	NA	NA	2.8	2.2	0.6

Location; (reference)	Study period	Incidence of influenza A(H1N1 & H3N2)-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza B-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza (all types and sub-types)-associated hospitalised ALRI (per 1000 children per year)		
		Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months
Multistate, USA (Dawood et al., 2010)	2008	NA	NA	NA	NA	NA	NA	4	2.9	0.8
	2004-2005	NA	NA	NA	NA	NA	NA	0.9	0.6	0.3
	2005-2006	NA	NA	NA	NA	NA	NA	0.9	0.7	0.4
	2006-2007	NA	NA	NA	NA	NA	NA	0.7	0.5	0.3
	2007-2008	NA	NA	NA	NA	NA	NA	1.1	0.8	0.4
Europe										

Location; (reference)	Study period	Incidence of influenza A(H1N1 & H3N2)-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza B-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza (all types and sub-types)-associated hospitalised ALRI (per 1000 children per year)		
		Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months
	2001-2002	NA	NA	NA	NA	NA	NA	NA	NA	1.2 *
Gipuzoka, Spain (Montes et al., 2005)	2002-2003	NA	NA	NA	NA	NA	NA	NA	NA	0.1 †
	2003-2004	NA	NA	NA	NA	NA	NA	NA	NA	1.5*
South-East Asia										
Sa Kaeo and Nakhon Phanom, Thailand (Simmerman and	2005	NA	NA	NA	NA	NA	NA	9.2	10.0	7.1
	2006	NA	NA	NA	NA	NA	NA	2.1	3.2	2.5

NA- Data not available

* Circulating strain A/H3N2

† Circulating strain A/H1N1 and Influenza B

Location; (reference)	Study period	Incidence of influenza A(H1N1 & H3N2)-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza B-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza (all types and sub-types)-associated hospitalised ALRI (per 1000 children per year)		
		Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months
colleagues, unpublished)	2007	NA	NA	NA	NA	NA	NA	7.4	7.2	4.5
	2008	NA	NA	NA	NA	NA	NA	5.2	8.3	7.1
Western Pacific										
Bohol, Philippines (Lucero and colleagues, unpublished)	2000-2001	1.1	1.1	NA	0	0	NA	1.1	1.1	NA
	2001-2002	1	0.8	NA	0.7	0.4	NA	1.7	1.1	NA
	2002-2003	1.7	1.3	NA	1.4	0.8	NA	3.1	2.1	NA
	2003-2004	1.8	2.2	NA	0.9	0.7	NA	2.7	2.9	NA
Hong Kong SAR, China	2003-	7.8	5.5	7	0	0	0.5	7.8	5.5	7.5

Location; (reference)	Study period	Incidence of influenza A(H1N1 & H3N2)-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza B-associated hospitalised ALRI (per 1000 children per year)			Incidence of influenza (all types and sub-types)-associated hospitalised ALRI (per 1000 children per year)		
		Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months	Age 0-11 months	Age 0-23 months	Age 0-59 months
(Chiu et al., 2009)	2004									
	2004-2005	10.4	7.3	5.4	0	1.3	3.1	10.4	8.7	8.5
	2005-2006	3.9	4.7	4.1	0	0	1.6	3.9	4.7	5.7
Suzhou district, China (Ji et al., 2010)	2007	NA	NA	NA	NA	NA	NA	0.6	0.3	0.2
	2008	NA	NA	NA	NA	NA	NA	0.6	0.4	0.3

Table 6: Estimates of incidence (per 1000 children) and number of new hospitalised cases of influenza-associated ALRI in children younger than 5 years in 2008, by World Health Organization Regions

WHO Region (number of studies)	Incidence of influenza-associated hospitalised ALRI in infants aged below 1 year (95% CI) *	Number of new episodes in infants aged below 1 year in 2008 (thousands)	Incidence of influenza-associated hospitalised ALRI in children aged below 5 years (95% CI)*	Number of new episodes in children aged below 5 years in 2008 (thousands)
Africa (6)	2.3 (1.6, 3.4)	64 (44, 92)	1.0 (0.9, 1.2)	134 (113, 159)
Americas (16)	2.5 (1.8, 3.6)	39 (28, 55)	1.2 (1.0, 1.6)	95 (73, 126)
Europe (6)	1.9 (1.3, 2.8)	21 (15, 31)	1.1 (0.7, 1.6)	55 (37, 82)
South East Asia (4)	2.2 (0.7, 6.8)	79 (25, 247)	1.4 (0.4, 5.6)	257 (65, 1020)
Western Pacific (7)	3.6 (1.7, 7.4)	81 (39, 169)	2.1 (0.9, 5.1)	255 (105, 620)
Summed regional estimate †		284 (151, 594)		796 (393, 2006)
Developing countries (21)	2.8 (2.0, 4.1)	348 (239, 507)	1.4 (0.9,2.3)	844 (566, 1269)
Industrialised countries (18)	2.4 (1.7, 3.0)	26 (20, 33)	1.2 (0.9, 1.7)	67 (50, 87)
Global estimate (39) ‡		**373 (258, 540)**		**911 (617, 1356)**

* Data are incidence meta-estimates from random effects model; incidence estimates are per 1000 children per year

† There is no regional estimate for Eastern Mediterranean region as there are no data from this region. This contributes to the difference in summed regional estimates and global estimates.

‡ Number of new cases globally in the year 2008 is the sum of new cases in children residing in developing and industrialised countries in 2008; data in parentheses are 95% CIs

3.1.2. Prevalence-based approach

3.1.2.1. Proportion of hospitalised ALRI cases positive for influenza

3.1.2.1.1. Methods

3.1.2.1.1.1. Literature search

A systematic literature review (using the same search strategy as detailed in Appendix A3) was conducted across the following electronic databases – Medline (Ovid), Embase, CINAHL, Global Health, Web of Science, WHOLIS, LILACS, IndMed; and a grey literature database (SIGLE). The search was limited to studies published between 1 January, 1995, and 31 December, 2011 for the reasons already detailed in section 3.1.1.1.1. In this instance, Chinese language databases were not searched, as the assistance of a Chinese researcher was no longer available. In order to conform to the PRISMA guidelines, a parallel literature search in English language databases and data extraction was independently performed by another researcher (Kathryn Lafond, MPH) based at US CDC. For defining influenza-associated hospitalised ALRI, a case definition identical to that for incidence based studies was utilised –i.e. a child with cough or difficulty breathing hospitalised for respiratory ailment and testing positive for influenza virus (using valid diagnostic tests). All identified studies were assessed using the eligibility criteria detailed in Panel 3. No language or publication restrictions were applied. Data were extracted onto a data extraction template designed on Microsoft Excel (Microsoft office 2003). Any disagreements were discussed and arbitrated by a senior researcher at US CDC (Dr. Marc-Alain Widdowson). Since the US CDC was leading the efforts to collect unpublished data relating to prevalence-based disease burden estimates, and the author was collaborating on this project, it was decided that (for the doctoral thesis), the estimates for proportion of hospitalised ALRI positive for seasonal influenza would be based only on data from systematic review of published literature.

Inclusion criteria

- Studies with data on children aged less than 5 years with laboratory confirmed influenza and hospitalised for ALRI
- Studies published between 1 January 1995 and 31 December 2011
- Study should have been carried out for a minimum of one year (except in temperate regions where influenza seasonality is more clearly defined)

Exclusion criteria

- Studies where influenza was studied as a co-infection rather than a primary outcome
- Studies that reported a denominator population at risk and were thus able to compute incidence rates
- Case definition was not clearly defined and / or not consistently applied
- Studies reporting data for age groups other than the full 0-59 month age range
- Study data after 21 April, 2009 (onset of influenza A(H1N1)pdm09 pandemic
- Case ascertainment was conducted only during an epidemic period

Panel 3: Eligibility criteria for selection of studies reporting the proportion of hospitalised ALRI cases positive for seasonal influenza in young children

3.1.2.1.1.2. Ethical approval

The author conducted a Self-Audit for Level 1 Ethical Review in relation to this project. This was done using a checklist developed by the School of Health in Social Science and adopted by the Post Graduate Ethics Committee of the College of Medicine and Veterinary Medicine, University of Edinburgh. Since no foreseeable ethical risks were identified (as all analysis were on secondary data), a formal ethical approval was not required. The individual collaborating sites re-analysing primary data sought ethical approvals from their respective Institutional Review Boards. A copy of the Self-Audit Checklist for Level 1 is placed in the Appendix A1.

3.1.2.1.1.3. Statistical analysis

A meta-analysis of the data (through April 15, 2009) from studies reporting proportion of hospitalised ALRI cases positive for seasonal influenza was conducted (using Stata 11.2) and

the pooled estimates along with 95% CIs have been reported. As discussed previously in section 3.1.1.1.5.3, the random effects model (DerSimonian-Laird method) was used since heterogeneity in the data was anticipated. The proportion of influenza positive hospitalised ALRI cases was estimated by regions- both for industrialised and developing countries as well as for the six WHO regions.

3.1.2.1.2. Results

Twenty three hospital-based published studies using passive case ascertainment (i.e. a child with ALRI being brought to a health facility) and satisfying the eligibility criteria were identified (Figure 11). All studies were in large tertiary care centres in urban areas (Table 7). Nineteen of the 23 included studies were from developing countries (Figure 12). The data from both the developing as well as industrialised countries were significantly heterogeneous ($p<0.0005$, I^2 >90 percent). Only 42% of the included studies from developing countries used PCR (six studies) or viral culture (two studies) for identification of the influenza virus. Two additional studies used viral culture in combination with immunofluorescence to identify viral infection. By contrast, 50% (2/4) of the studies from industrialised countries used PCR as a diagnostic assay. The two remaining studies used viral culture in combination with immunofluorescence to identify viral infection. There was substantial variability in the proportion of hospitalised ALRI cases positive for influenza. In general, the proportion of influenza positive hospitalised ALRI cases was highest in the Western Pacific region (Table 8). The proportion of influenza positive hospitalised ALRI cases in young children was about 5.0 (95% CI 3.6 to 7.0) percent in developing countries and about 8.4 (95% CI 4.2 to 16.7) percent in industrialised countries (Figure 13). Eleven studies (8 from developing countries), reported on influenza positivity separately for the influenza A virus (Johnson et al., 2008, Smuts, 2008, Venter et al., 2011, Carballal et al., 2001, Viegas et al., 2004, Aranda-Romo et al., 2010, Bakir et al., 1998, Foulongne et al., 2006, Weigl et al., 2005b, Wolf et al., 2006, Samransamruajkit et al., 2008). Data from these studies indicate that influenza A conferred 70 to 100 percent of the disease burden due to seasonal influenza-associated hospitalised ALRI in young children.

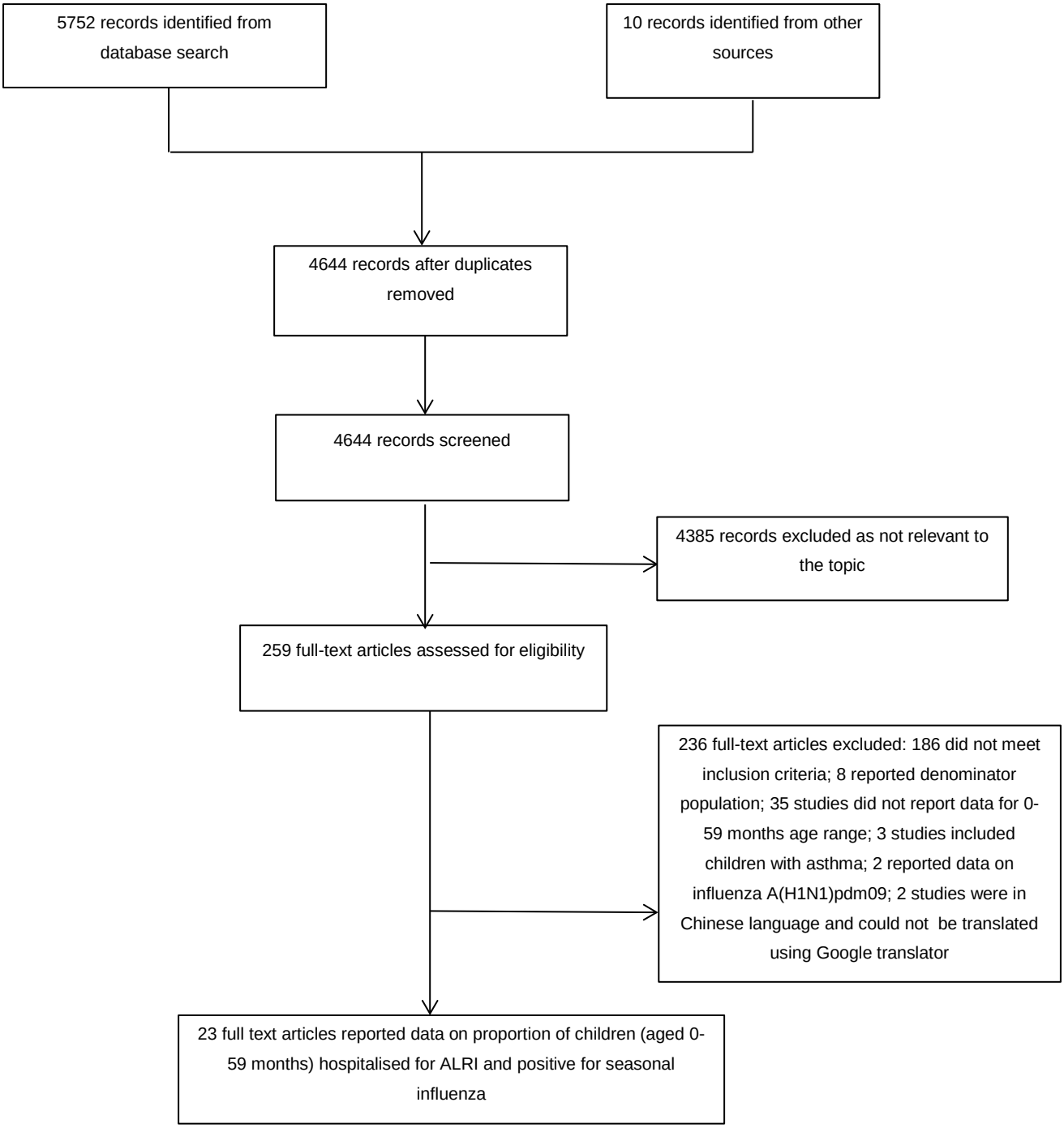

Figure 11: Flow diagram for selection of studies (in young children) reporting proportion of hospitalised ALRI cases positive for seasonal influenza

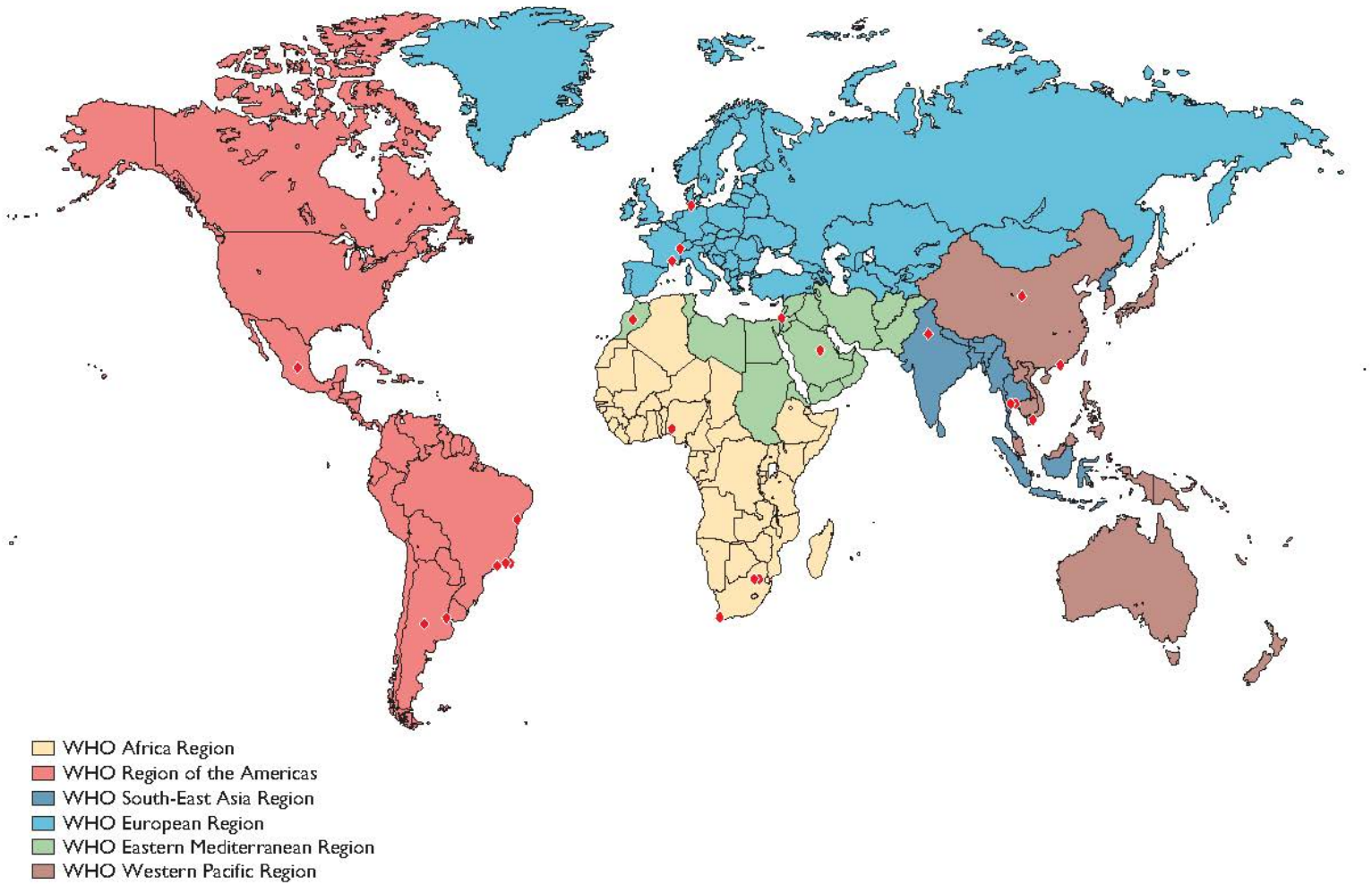

Figure 12: Location of the 23 studies (indicated using red diamonds) reporting proportion of influenza positive hospitalised ALRI cases in young children by World Health Organization Regions

Table 7: Proportion of hospitalised ALRI cases in children (aged 0-59 months) positive for seasonal influenza

Location (reference)	Study period	Case definition	Specimen and Diagnostic test(s)	Proportion (%) of hospitalised ALRI in children aged below 5 years positive for seasonal influenza (n)
Africa				
Ibadan, Nigeria (Johnson et al., 2008)	1992-1995	Hospitalised ALRI with a chest radiograph suggestive of pneumonia	Nasopharyngeal aspirate; IFA	15.6 (50/323)
Soweto, South Africa (Madhi et al., 2000)	1997-1998	Hospitalised ALRI	Nasopharyngeal aspirate; DFA, viral culture	8.6 (70/817)
Cape Town, South Africa (Smuts, 2008)	2003-2004	Hospitalised ALRI	Nasopharyngeal aspirate, tracheal aspirate, bronchoalveolar lavage; IFA	0.9 (9/1055)
Pretoria, South Africa (Venter et al., 2011)	2006-2007	Hospitalised ALRI	Nasopharyngeal aspirate; DFA, multiplex PCR	5.0
Americas				
Rio de Janerio, Brazil (Sutmoller et al., 1995)	1987-1989	Hospitalised ALRI	Nasopharyngeal aspirate; IFA	1.4 (7/501)
Multicentre, Argentina (Carballal et al., 2001)	1993-1994	Hospitalised ALRI	Nasopharyngeal aspirate; IFA	2.4 (29/1234)
Buenos Aires City and Greater Buenos Aires, Argentina (Viegas et al., 2004)	1998-2002	Hospitalised ALRI	Nasopharyngeal aspirate; IFA	2.8 (531/18561)
San Luis Potosi, Mexico (Aranda-Romo et al., 2010)	2002-2009	Hospitalisation for respiratory symptoms	Nasal wash; RT-PCR	4.4 (106/2378)
Sao Paulo, Brazil (Thomazelli et al., 2007)	2003	Hospitalised ALRI	Nasal wash; RT-PCR	5.1 (17/336)
Salvador, Brazil (Nascimento-Carvalho et al., 2008)	2003-2005	Hospitalised ALRI with chest radiograph compatible with pneumonia	Nasopharyngeal aspirate; IFA	9.2 (17/184)
Sao Paulo, Brazil (Pecchini et al., 2008)	2005-2006	Hospitalised ALRI	Nasopharyngeal aspirate; IFA	3.3 (15/455)
Eastern Mediterranean				
Riyadh, Saudi Arabia (Bakir et al., 1998)	1993-1996	Hospitalised ALRI	Nasopharyngeal aspirate; IFA and viral culture	3.1 (45/1429)
Multicentre, Morocco (Barakat et al., 2011)	2007-2009	SARI: Hospitalised for cough or difficulty breathing with or without wheezing or stridor in a calm child, or chest indrawing	Oro-pharyngeal and naso-pharyngeal swabs; IFA	1.3 (9/696)

Location (reference)	Study period	Case definition	Specimen and Diagnostic test(s)	Proportion (%) of hospitalised ALRI in children aged below 5 years positive for seasonal influenza (n)
Europe				
Beer-Sheva, Israel (Wolf et al., 2006)	2001-2002	Hospitalised ALRI	Nasal wash; DFA, viral culture	15.1 (78/516)
Kiel, Germany (Weigl et al., 2005a)	2002-2004	Hospitalised ALRI (Discharge diagnosis ICD-9 code 460 to 490, and ICD-10 J00 to J22)	Nasopharyngeal aspirate; multiplex RT-PCR	7.2 (32/443)
Montpellier, France (Foulongne et al., 2006)	2003-2004	Hospitalised ALRI	Nasopharyngeal aspirate; DFA and viral culture	3.1 (18/589)
Lausanne and Geneva, Switzerland (Cevey-Macherel et al., 2009)	2003-2005	Hospitalised ALRI	Nasopharyngeal aspirate; RT-PCR	14.1 (14/99)
South East Asia				
New Delhi, India (Kabra et al., 2003)	1995-2003	Hospitalised ALRI	Nasopharyngeal aspirate; viral culture	5.3 (5/95)
Bangkok, Thailand (Suntarattiwong et al., 2007)	2004-2005	Hospitalised ALRI	Nasopharyngeal swab; viral culture	8.6 (39/456)
Bangkok, Thailand (Samransamruajkit et al., 2008)	2006-2007	Hospitalised ALRI	Nasopharyngeal swab; RT-PCR	11.3 (27/239)
Western Pacific				
Lanzhou, Gansu, China (Zhang et al., 2011)	2004-2005	Hospitalised ALRI with chest radiograph compatible with pneumonia	Nasopharyngeal swab; DFA	8.4 (58/688)
Ho Chi Minh City, Vietnam (Do et al., 2011)	2004-2008	Hospitalised ALRI	Nasal swabs, throat swabs and Nasopharyngeal aspirate; multiplex RT-PCR	15.9 (47/295)
Hong Kong SAR, China (Tsung et al., 2010)	2005-2007	Hospitalised ALRI	Nasopharyngeal aspirate and nasal swabs; Multiplex RT-PCR	11.3 (53/469)

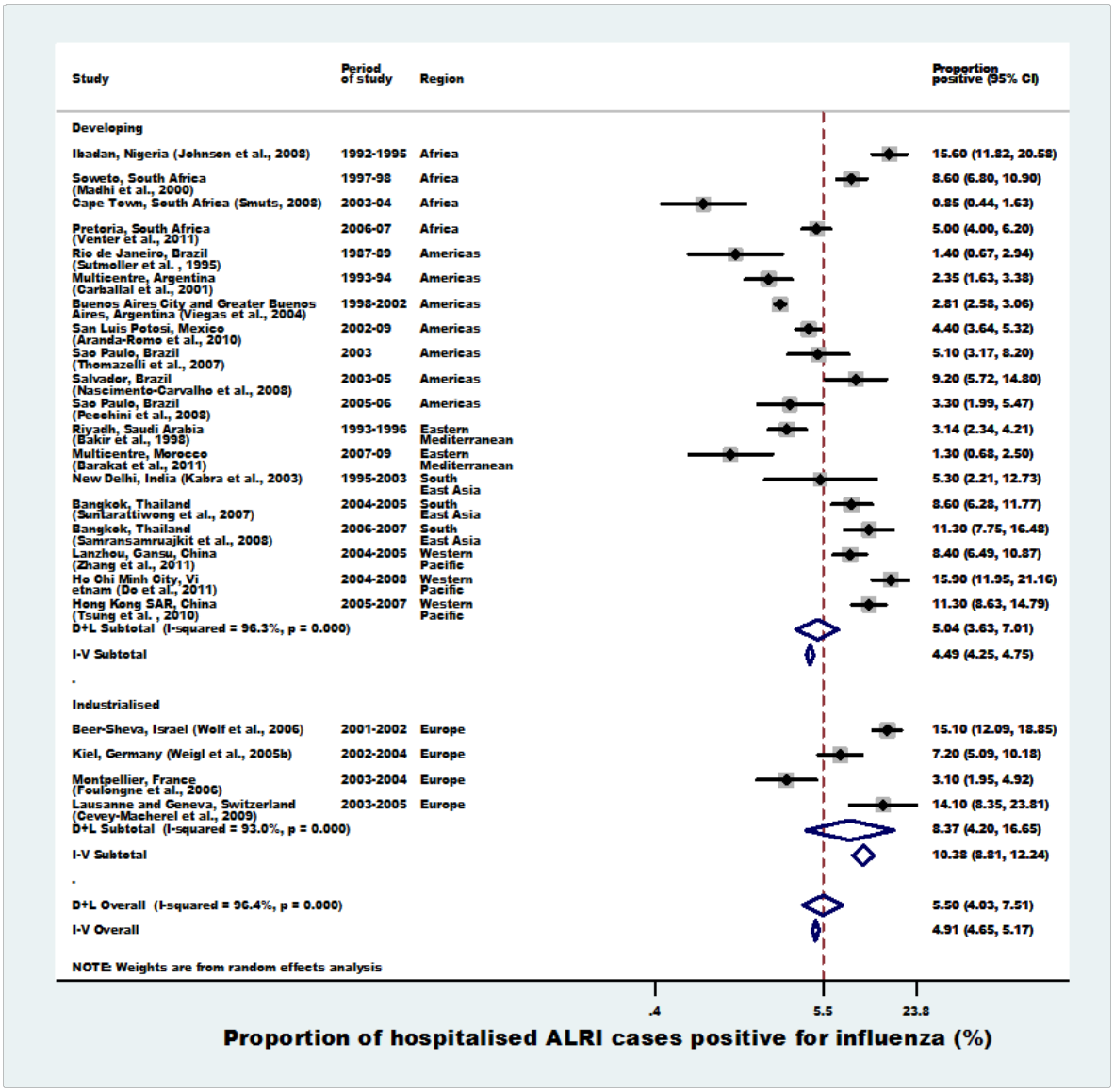

Figure 13: Forest plot of estimates of proportion of hospitalised ALRI cases positive for seasonal influenza in young children

D+L (overall) indicates meta-estimate by random effects analysis

I-V (overall) indicates meta-estimate by fixed effects analysis

Table 8: Meta-estimates of the proportion of influenza positive hospitalised ALRI cases in young children by World Health Organization Regions

WHO Region (Number of studies)	Proportion (%) of hospitalised ALRI cases positive for influenza (95% CI) *
Africa (4)	5.2 (2.4 to 11.1)
Americas (7)	3.6 (2.6 to 4.9)
Eastern Mediterranean (2)	2.1 (0.9 to 5.0)
Europe (4)	8.4 (4.2 to 16.7)
South East Asia (3)	9.1 (6.8 to 12.3)
Western Pacific (3)	11.4 (7.9 to 16.3)
Developing countries (19)	5.0 (3.6 to 7.0)
Industrialised countries (4)	8.4 (4.2 to 16.7)

* Data are proportion meta-estimates from random effects model

3.1.2.2. Number of hospitalised ALRI cases in young children in 2008

3.1.2.2.1. Methods

3.1.2.2.1.1. Literature search

A systematic literature review was conducted across the following electronic databases – Medline (Ovid), Embase, CINAHL, Global Health, Web of Science, WHOLIS, LILACS, and IndMed. Additionally, three Chinese language databases (The China National Knowledge Infrastructure or CNKI (www.global.cnki.net), Wanfang (http://www.wanfangdata.com.cn), and Chongqing VIP (http://www.cqvip.com) were searched for studies (with a clear denominator of the population at risk) published in Chinese language during the same period. A grey literature database (SIGLE) was also searched. The detailed search strategy is placed in the appendix (Appendix A4). The search was limited to studies published between 1 January, 1990, and 31 March, 2012. Studies published since January 1990 (rather than since January 1995 as was in the case of search for influenza-associated hospitalized ALRI) were included because identification of hospitalised ALRI cases were not based on diagnostic assays. Extending the search period would therefore permit inclusion of some important studies that were conducted in the latter part of 1980s and early part of 1990s, thereby increasing the final number of studies included in the meta-analysis. Panel 4 shows the eligibility criteria. No language or publication restrictions were applied. Only studies that reported a well-defined catchment population or were able to estimate the population at risk were included. In addition to the author, the literature search and data extraction from English language databases was conducted independently by another researcher (Peter Hanlon, MBChB). Any disagreements were resolved after discussion with the supervisor for this doctoral thesis (Prof. Harry Campbell). Literature search and data abstraction from Chinese language databases were performed by another researcher Jian Shayne F. Zhang, MPH who read Chinese as a first language and had access to all three databases. The search strategy and data extraction were validated during direct discussions with the author. All data were extracted onto data extraction template designed on Microsoft Excel (Microsoft Office 2003).

Inclusion criteria

- Studies reporting hospitalisation for ALRI in children younger than five years
- Studies with at least 12 consecutive months of data collection
- Studies published between January 1990 and March 2012
- Studies in children less than 5 years of age, or should have reported data for this age group separately
- Studies reporting hospitalised ALRI incidence / mortality for at least the first year of life

Exclusion criteria

- Studies reporting only aetiology-specific incidence or mortality estimates
- Studies reporting incidence or mortality estimates for ALRI confirmed only by a chest radiograph
- Studies where description of the methods for estimating denominator population was not clear
- Case definition not clearly defined and / or not consistently applied
- Incidence and mortality estimated using modelling techniques

Panel 4: Eligibility criteria for selection of studies reporting incidence of hospitalised ALRI in young children

3.1.2.2.1.2. Unpublished data

Twenty three leading researchers on paediatric pneumonia were identified through their publication track record as well as through extensive consultations with subject experts-primarily those involved in the RSV and Influenza-associated ALRI disease burden estimation projects. This led to the formation of an international consortium ("Severe ALRI Working Group" (SAWG)) that consisted primarily of researchers working in developing countries. The author organised and led a two-day meeting of SAWG in Edinburgh, UK on August 30-31, 2010. This meeting was funded by the World Health Organisation's Global Influenza Programme.

During the two-day meeting, the SAWG discussed extensively the availability of data on hospitalised ALRI (from studies having a clear denominator of the population at risk) in

children aged below five years and finalised common case definitions for analysing all available data. The group agreed to either re-analyse their already published data or share hitherto unpublished data from on-going studies on a common data extraction template designed in Microsoft Excel 2003. The group suggested the inclusion of some other research groups who, to the best of their knowledge, had conducted similar studies but were not invited for the meeting. These groups were contacted and enlisted into the SAWG. Finally, 24 research sites from 16 countries contributed unpublished data for estimating the incidence of hospitalised (all-cause) ALRI in children aged 0-59 months.

3.1.2.2.1.3. Case definitions

Most investigators used modified versions of WHO case definitions for pneumonia (Table 9) (World Health Organization, 1991, Department of Child and Adolescent Health, 2005). However, for this thesis, the term ALRI rather than pneumonia has been chosen since a large proportion of ALRI in young children present as bronchiolitis which may often be clinically indistinguishable from pneumonia. It was decided that children with cough or difficulty breathing with increased respiratory rate for age with / without lower chest wall indrawing that were hospitalised (based on the judgement of the attending physician) should be referred to as hospitalised ALRI.

3.1.2.2.1.4. Ethical approval

The author conducted a Self-Audit for Level 1 Ethical Review in relation to this project. This was done using a checklist developed by the School of Health in Social Science and adopted by the Post Graduate Ethics Committee of the College of Medicine and Veterinary Medicine, University of Edinburgh. Since no foreseeable ethical risks were identified (as all analysis were on secondary data), a formal ethical approval was not required. The individual collaborating sites re-analysing primary data sought ethical approvals from their respective Institutional Review Boards. A copy of the Self-Audit Checklist for Level 1 is placed in the Appendix A1.

3.1.2.2.1.5. Statistical analysis

3.1.2.2.1.5.1. Data imputation

While fifty one of the 85 studies included in this review provided data for infants (0-11 months) and 66 studies provided data for the young children (0-59 months), only 43 studies provided data for both age ranges (0-11 months and 0-59 months). In order to deal with the

missing data in the remaining 42 studies, data imputation was performed separately for the developing and industrialised regions by calculating the median incidence rate ratio (IRR) as was previously done in similar studies by Rudan and Nair (Rudan et al., 2004, Nair et al., 2010). For imputing missing data, it was assumed that the age structure is similar across all studies from a given region (i.e. developed or industrialised countries).

Using data from 17 published and 18 unpublished studies from developing countries, relative to an incidence rate of 1.0 in the age group 0-11 months, the median IRR for the age group 0-23 months and 0-59 months was calculated to be 0.75 and 0.37. This median IRR was then applied to the reported incidence rates of hospitalised ALRI for 0-11 months, 0-23 months or 0-59 months to estimate the incidence rate for the missing age groups. In the case of industrialised countries, data on full age range were available from 7 published studies and one unpublished study. Using incidence rate data from these studies, the median incidence rate ratio (IRR) was computed for children in the age group 0-23 months and 0-59 months. Relative to an incidence of 1.0 in the age group 0-11 months, the median IRR for the age group 0-23 months and 0-59 months was calculated to be 0.70 and 0.45. In order to assess the validity of data after imputation, a sensitivity analysis was conducted by including only those studies which had data for the full age range (0-59 months) (for results see Table 27).

3.1.2.2.1.5.2. Meta-analysis

A meta-analysis of the data (through December 31, 2008) from studies reporting incidence of hospitalised ALRI was conducted (using Stata 11.2) and the pooled estimates along with 95% CIs have been reported. As discussed in section 3.1.1.1.5.3, the random effects model (DerSimonian-Laird method) was used since heterogeneity in the data was anticipated (DerSimonian and Laird, 1986). The incidence rates were estimated by regions- for industrialised and developing countries as well as for the six WHO regions. These incidence estimates were then applied to the population of children younger than 5 years in 2008 both globally as well as in the six WHO regions to estimate the number of new episodes of hospitalised ALRI in 2008. Countries have been designated as industrialised or developing on the basis of UNICEF's classification (United Nations Children's Fund, 2012). The child population estimates for 2008 are as in the UN Population Division's database, "World Population Prospects: The 2010 revision" (http://esa.un.org/unpd/wpp/unpp/panel_population.htm).

3.1.2.2.1.5.3. Adjustments

One published study (study period 1998-2005) was identified from Soweto, South Africa (Madhi et al., 2005). Since HIV is a major risk factor for hospitalised ALRI, and the prevalence of HIV in children aged below 5 years has decreased substantially and access to highly active antiretroviral treatment (HAART) has increased dramatically in South Africa from 2002 (median year for the included study from Soweto, South Africa), the reported incidence rates for this study (Table 9) were adjusted (as described in Appendix A5) taking into consideration both paediatric HIV prevalence (in children aged below 5 years) and access to HAART using data for Soweto obtained from National Institute of Communicable Diseases, South Africa (Madhi, 2011). The adjusted rates were used while conducting the meta-analysis.

If the duration of any eligible study was not in exact multiples of one year (e.g. 18 months, 30 months etc.), the annualised incidence rate has been calculated and reported by adjusting for the population at risk.

3.1.2.2.2. Results

Eighty five hospital-based studies with incidence data satisfied the eligibility criteria (Figure 14). Of these, 61 were published studies (14 of them in Chinese language) and 24 were unpublished studies with data collected through 15 April 2009 (Figure 15). Twenty nine studies were in rural populations, sixteen in urban and the remainder were a mixture of rural and urban populations. Forty percent (24/61) of studies from developing countries were either cohort studies or were nested in a demographic surveillance site; 8% (5/61) had a well-defined catchment area and the population was estimated using a healthcare utilization survey (Azziz-Baumgartner et al., 2012, Jordan et al., 2009, Feikin et al., 2011); and 52% (32/61) of the studies were based in hospitals with a well-defined catchment area (Table 9). Only 43 studies (24 published and 19 unpublished) reported incidence rates by age group for the full age range (i.e. 0-59 months) and data were imputed for the remaining 42 studies.

The majority of the data (25/85 studies) were from the Western Pacific Region of the WHO. Only two studies (both from Pakistan) were identified from the Eastern Mediterranean Region. There was considerable variation in the incidence rates across the six WHO regions (Table 10). While the incidence rates for infants (aged 0-11 months) were highest in Africa and South-East Asia regions (about 49 episodes per 1000 children / year), the overall incidence for young children was highest in Africa (about 21 episodes per 1000 children / year). The data from developing and industrialised countries were significantly heterogeneous ($p<0.0005$, $I^2>93$ percent).

Sixty-one hospital-based studies from developing countries reported incidence of hospitalised severe ALRI in children aged 0-59 months. The incidence of hospitalised severe ALRI in young children aged 0-59 months was 18.9 (95% CI 15.9 to 22.4) episodes per 1000 children per year in developing countries (Table 10). The incidence rates were highest in infants aged 0-11 months [48.6 (95% CI 41.0 to 57.6) episodes per 1000 children per year]. Using data from 24 hospital-based studies in industrialised countries, the incidence of hospitalised severe ALRI in children aged 0-11 months and 0-59 months residing in industrialised countries was estimated to be 19.1 (95% CI 15.7 to 23.4) episodes and 9.6 (95% CI 7.1 to 13.0) episodes per 1000 children per year. This translates to about 11.3 (95% CI 9.5 to 13.5) million episodes of hospitalised ALRI worldwide in children aged less than 5 years in 2008, with disease in infants (0-11 months) contributing to about 52% of this overall “burden” (Table 10).

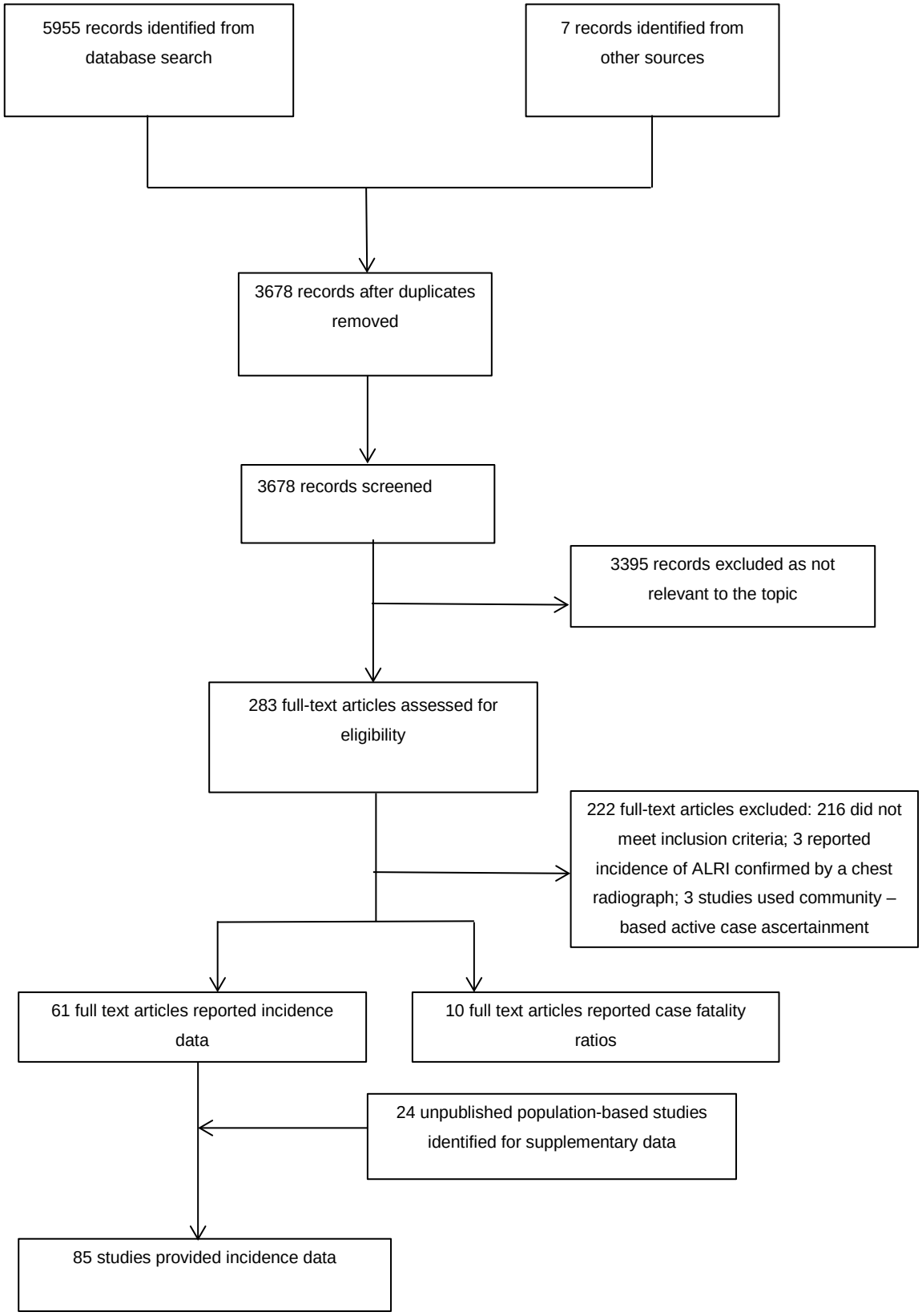

Figure 14: Flow diagram for selection of studies reporting incidence of hospitalised ALRI in young children

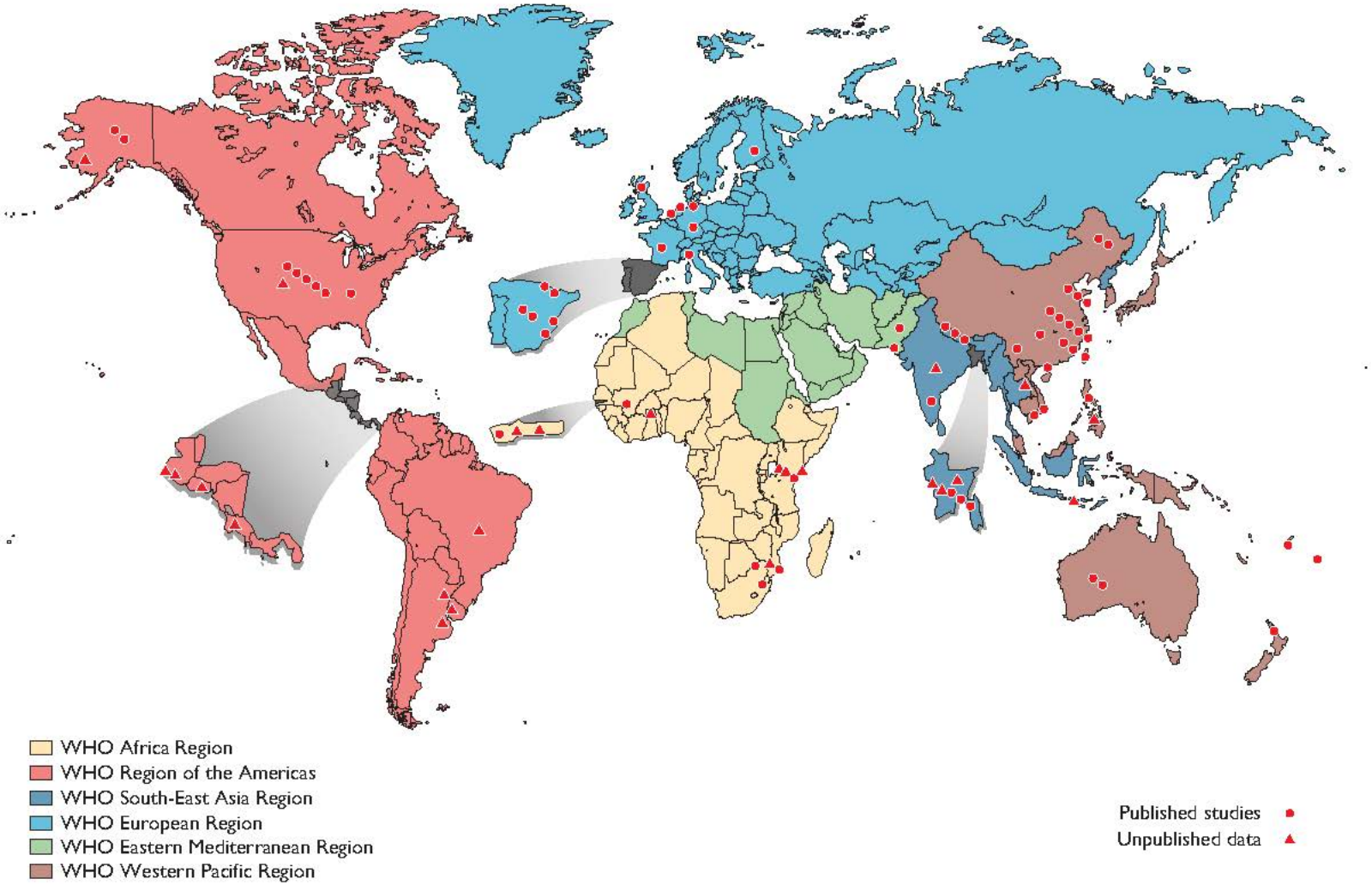

Figure 15: Location of the 85 studies reporting incidence of hospitalised ALRI by World Health Organization Regions

Table 9: Incidence estimates of hospitalised ALRI in children younger than 5 years from published and unpublished studies by World Health Organization Regions

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
Africa				
Kassena-Nankana District, Ghana; rural; 1990-1991 (Morris and colleagues, unpublished)	Defined population base (n=1439)	Physician diagnosed ALRI	56.8	20.9
Western Region, The Gambia; mixed rural-urban; 1993-1996 (Mulholland et al., 1997) ‡	Defined population base (n=21358)	Physician diagnosed ALRI	(21.6)	(8)
Soweto, South Africa; urban;1998-2001 (Madhi et al., 2005) § **	Defined population base (n=19914)	Physician diagnosed ALRI	(96.5)	35.7
Manhiça, Mozambique; rural; 1999-2000 (Robertson et al., 2004)	Defined population base (n=6020)	Physician diagnosed ALRI	126	68
Bamako, Mali; urban; 2000 (Campbell et al., 2004)	Census-derived estimate (n=200160)	Physician diagnosed ALRI	10	3.5
Agincourt, South Africa; rural; 2000-2001 (Robertson et al., 2004)	Defined population base (n=8258)	Physician diagnosed ALRI	332	80
Bondo district, Kenya; rural; 2001-2003 (Tornheim et al., 2007)	Census-derived estimate (n=52200)	Physician diagnosed ALRI	13.7	7
Upper River Division and Central River Division, The Gambia; rural; 2002-2004 (Zaman and colleagues, unpublished) ‡	Defined population base (n=5040)	Cough or difficulty breathing and chest wall indrawing or grunting	27.8	(10.3)

* ALRI= acute lower respiratory infection

† Data in parentheses are computed incidence estimates from data imputation

‡ Included children from 2 months of age

§ Excluded neonates (0-27 days)

** Incidence rates adjusted for HIV prevalence (0-59 months) and HAART coverage in 2008 included in meta-analysis

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
Kilifi District, Kenya; rural; 2002-2008 (Moisi and colleagues, unpublished) ††	Defined population base (n=45600)	Acute cough / difficulty in breathing AND chest wall indrawing or tachypnea (>60 breaths per minute) in infants aged <2 months	61.1	19.9
Manhiça district, Mozambique; rural; 2004-2006 (Roca and colleagues, unpublished)	Defined population base (n=4954)	Age≥2 months- cough or difficult breathing with chest wall indrawing in hospitalised children. Age<2 months- cough or difficult breathing with tachypnea or chest wall indrawing	65.3	(24.2)
Bondo district, Nyanza province, Kenya; rural; 2007-2009 (Ope and colleagues, unpublished)‡	Census-derived estimate (n=160417)	Physician diagnosed ALRI	28.6	16.8
Upper River Region, The Gambia; rural; 2008-2009 (Mackenzie and colleagues, unpublished)‡	Defined population base (n=27086)	Physician diagnosed ALRI OR Cough or difficult breathing with chest wall indrawing	86.4	33.2
Lwak, Kisumu, Kenya; rural; 2008-2009 (Breiman and colleagues, unpublished)	Census-derived estimate (n=4215)	Physician diagnosed ALRI OR Age ≥2 months- Cough or difficult breathing with chest wall indrawing; Age <2 months- Tachypnea (>60 breaths/ min) or chest wall indrawing	72.9	98.9
Americas				
American Indians and Alaska Natives, USA; rural; 1990-1995 (Lowther et al., 2000)	Census-derived estimate (n=678782)	Hospitalised bronchiolitis (Discharge diagnosis- ICD-9-CM code 466.1)	61.4	11.3
Tennessee (TN), USA; mixed rural-urban; 1995-2008 (Carroll et al., 2008)	Census-derived estimate (n=12260)	Hospitalised bronchiolitis (Discharge diagnosis- ICD-9 CM code 466.1 and / or 480.1)	70.7	(31.8)
USA; mixed rural-urban; 1997–1999 (Grijalva et al., 2010) ‡‡	Census-derived estimate	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 480-487.0)	15	7.4
USA; mixed rural-urban; 1996-1998(Henrickson et al., 2004)	Census-derived estimate	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 480-487.0)	(40.4)	18.2
USA; mixed rural-urban; 1997-2000 (Lee et al., 2010)	Census-derived estimate (n=48127200)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 480-487.0)	11.6	5.2

†† Day 0 excluded

‡‡ Detailed age specific incidence estimates obtained directly from authors

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
American Indians and Alaska Natives, USA; rural; 1999-2001(Peck et al., 2005) §	Census-derived estimate (n=348486)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 466.1 and / or 480 - 486)	128.7	32.9
Colorado (CO), USA; mixed rural-urban; 2000-2008 (Simoes and colleagues, unpublished)	Census-derived estimate (n=374169)	Physician diagnosed ALRI	43.1	16.9
Monroe County (NY), Davidson County (TN) and Hamilton County (OH), USA; mixed rural-urban; 2000-2004 (Weinberg et al., 2009)	Census-derived estimate (n=183839)	Physician diagnosed ALRI	43.9	15.2
USA; mixed rural-urban; 2001–2007 (Grijalva et al., 2010) ‡‡	Census-derived estimate	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 480-487.0)	10.2	5.8
Paysandú and Salto, Uruguay; mixed rural-urban; 2001-2004 (Hortal and colleagues, unpublished)	Census-derived estimate (n=61950)	Physician diagnosed ALRI	77.8	34.5
Yukon Kuskokwim Delta, Alaska, USA; rural; 2001-2007 (Singleton and colleagues, unpublished)	Census-derived estimate (n=1850)	Hospitalised ALRI (Discharge diagnosis- ICD-9CM code 480-486, 507.0 and 487.0)	223.4	(82.6)
Concordia and Parana, Argentina; urban; 2002 - 2005 (Ruvinsky and colleagues, unpublished)	Census-derived estimate (n=12500)	Acute cough / difficulty in breathing AND chest indrawing or tachypnea (>60 breaths per minute) in infants aged <2 months	30.3	14.2
San Lorenzo & Comitancillo, Guatemala; rural; 2002-2004 (Bruce and colleagues, unpublished) §§	Defined population base (n=518)	Cough or difficult breathing with lower chest wall indrawing in children >2 months of age OR cough or difficult breathing with tachypnea (60 breaths / min.) in a child <2 months of age	49.8	(18.4)
United States; 2003 (Yorita et al., 2008)	Census-derived estimate	Physician diagnosed ALRI (Discharge code ICD-9-CM 022.1, 031.0, 033, 095.1, 466, 480-487, 510, 511.1, 513, 517.1, 770.0)	41.4	18.6
Pilar, (Buenos Aires Province), Argentina; mixed rural-urban; 2003 -2005 (Gentile and	Census-derived estimate (n=40814)	Physician diagnosed ALRI	35.5	10.5

§§ All eligible subjects were followed up weekly at home by trained field workers who referred children with findings suggestive of respiratory disease to the community clinics and 70-80% of these were attended by a physician

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
colleagues, unpublished)§				
USA; mixed rural-urban; 2003-2006 (Lee et al., 2010)	Census-derived estimate	Physician diagnosed ALRI (Discharge diagnosis ICD-9 CM code 480-487.0)	9.3	4.8
San José, Costa Rica; urban; 2007-2009 (Arguedas and colleagues, unpublished)§	Census-derived estimate (n=64992)	Physician diagnosed ALRI	10	(3.7)
Goiânia, Brazil; urban; 2007-2009 (Andrade and colleagues, unpublished)§	Census-derived estimate (n=56146)	Physician diagnosed ALRI	58.4	(21.6)
Multicentre, El Salvador; mixed rural-urban; 2007-2008 (Clara and colleagues, unpublished)	Census-derived estimate (n=557088)	Hospitalised ALRI (Discharge diagnosis- ICD-10CM codes J10, J11, J09-J18.9, J20, J21, J22, J80, J96. For new-borns also P23-P23.9)	95.3	28
Santa Rosa, Guatemala; mixed rural-urban; 2007-2008 (McCracken and colleagues, unpublished)	Census-derived estimate (n=12700)	Physician diagnosed ALRI OR age 2-59 months- cough or difficulty breathing with chest wall indrawing; age < 2months- RR>60/min or chest wall indrawing	38.6	14.7
Eastern Mediterranean				
Multicentre, Pakistan; peri-urban; 2002-2003 (Nizami et al., 2006) ‡	Census-derived estimate (n=13364)	Cough or difficulty breathing plus any danger sign (inability to feed or drink, vomiting everything, convulsions, lethargy or unconsciousness) or chest wall indrawing or stridor	19.8	10.3
Karachi, Pakistan; mixed rural-urban; 2007- 2008 (Owais et al., 2010)	Defined population base (n=3950)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing or stridor or general danger signs (inability to breast feed or drink, vomits everything, convulsion, lethargy, loss of consciousness)	40	14.7
Europe				
Scotland, United Kingdom; mixed rural-urban; 1981-2005 (Roxburgh et al., 2008)	Census-derived estimate (n=7679789)	Physician diagnosed ALRI (Discharge code-ICD-9 CM 480-486.0 and ICD-10-AM J12-18)	3.7	2.2
Kuopio, Finland; mixed rural-urban; 1981-1982 (Jokinen et al., 1993) §	Census-derived estimate (n=2917)	Physician diagnosed ALRI	(41.9)	18.9
Spain; mixed rural-urban; 1995-1996 (Monge and Gonzalez, 2001)	Census-derived estimate (n=3213968)	Physician diagnosed ALRI (Discharge code- ICD-9 CM 480-486.0)	(11)	4.9

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
Spain; mixed rural-urban; 1995-1998 (Gil et al., 2002)	Census-derived estimate (n=7684928)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 003.22, 052.1, 055.1, 073.0, 083.0, 480-487.0)	(9.3)	4.2
Valencia, Spain; urban; 1995-2000 (Garces-Sanchez et al., 2005)	Defined population base (n=654)	Physician diagnosed ALRI	(15.6)	7
Valencia, Spain; mixed rural-urban; 1995–2001 (Comes Castellano et al., 2005)	Census-derived estimate (n=1582398)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 481, 485, 486)	(11.5)	5.2
Gipuzoka, Spain; mixed rural-urban;1996-2000 (Vicente et al., 2003)	Census-derived estimate (n=62800)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 466.1)	(22.5)	10.1
Kiel, Germany; urban; 1996-2000 (Weigl et al., 2005a)	Census-derived estimate (n=53655)	Physician diagnosed ALRI	11.1	6.8
Netherlands; mixed rural-urban;1999- 2000 (van Gageldonk-Lafeber et al., 2009)	Census-derived estimate (n=971471)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 480-486.0)	(6.9)	3.1
Multicentre, Germany; mixed rural-urban; 1999 -2001 (Forster et al., 2004) ‡‡	Census-derived estimate (n=2374600)	Physician diagnosed ALRI	51.7	(23.2)
Liguria, Italy; mixed rural-urban; 2000-2004 (Ansaldi et al., 2008)	Census-derived estimate (n=16973)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 480-487.0)	(9.2)	(4.1)
Gipuzoka, Spain; mixed rural-urban; 2004-2007 (Cilla et al., 2009)	Census-derived estimate (n=135135)	Physician diagnosed ALRI	46	(20.7)
Netherlands; mixed rural-urban; 2006-2007 (van Gageldonk-Lafeber et al., 2009)	Census-derived estimate (n=971471)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM code 480-486.0)	(7.6)	3.4
Limousin, France; mixed rural-urban; 2007-2008 (Che et al., 2010)	Census-derived estimate (n=7292)	Hospitalised bronchiolitis	17.7	(8)
South East Asia				
Matlab, Bangladesh; rural; 1988-1989 (Zaman et al., 1997)	Defined population base (n=503)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(145)	53.6
Kamalapur, Bangladesh; urban; 1999-2000 (Brooks et al., 2005) ‡^ ***	Defined population base (n=511)	Crepitations on inspiration, with respiratory rate >50 breaths / min, with chest wall indrawing or other danger signs (lethargy, cyanosis, inability to	(109.6)	(40.5)

^ Rates do not include cases with wheezing or rhonchi without crepitations (as these were labelled as bronchiolitis)

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
		drink)		
Lombok, Indonesia; rural; 1999-2002 (Gessner and colleagues, unpublished)	Defined population base (n=38653)	Cough or difficult breathing with chest wall indrawing OR infant aged < 2 months with increased respiratory rate (≥60 / min.)	83.6	(30.9)
Matlab, Bangladesh; rural; 1999-2001 (Baqui et al., 2007)	Defined population base (n=12451)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing or stridor or general danger signs (inability to breast feed or drink, vomits everything, convulsion, lethargy, loss of consciousness)	101.1	50.2
Bhaktapur, Nepal; mixed rural-urban; 2004-2007 (Chandyo et al., 2010) ‡	Defined population base (n=2100)	Cough and / or difficult breathing combined with lower chest wall indrawing and admittance to hospital	(11.7)	(4.3)
Kathmandu, Nepal; urban; 2004-2007 (Shah et al., 2009a) ‡^	Census-derived estimate (n=243345)	Cough and / or difficult breathing with or without tachypnea AND chest indrawing	(16.8)	6.2
Nakhon Phanom and Sa Kaeo provinces, Thailand; rural; 2004-2008 (Baggett and colleagues, unpublished)	Census-derived estimate (n=427163)	Hospitalised ALRI- children having evidence of acute infection (reported fever or chills, documented temperature >38.2ºC or <35.5ºC, or abnormal WBC count or abnormal differential count) and at least one sign or symptom of lower respiratory tract disease (abnormal breath sounds on chest auscultation, tachypnea, cough, sputum production, hemoptysis, chest pain, or dyspnea)	83.4	55.2
Mirzapur, Bangladesh; rural; 2004-2008 (Arifeen and colleagues, unpublished) §	Defined population base (n=41040)	Physician diagnosed ALRI - Cough or difficult breathing with / without chest wall indrawing OR infant aged < 2 months with increased respiratory rate (≥60 / min.)	73.9	19
Patan, Nepal; urban; 2005-2006 (Williams et al., 2009) ‡^	Census-derived estimate (n=56875)	Tachypnea AND chest wall indrawing	(17.1)	6.3
Multicentre, India; rural; 2005-2007 (Chandran and colleagues, unpublished) §	Defined population base (n=15460)	Cough or difficulty breathing or fast breathing or chest retractions or chest wall indrawing or nasal flaring or grunting or abnormal auscultation	69.3	(25.6)

*** All eligible subjects were followed up weekly at home by trained Field Research Assistants (FRAs) who referred children with findings suggestive of respiratory disease to the clinic

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
Bangalore, India; urban; 2006 (Shah et al., 2009b)	Census-derived estimate (n=150945)	Physician diagnosed ALRI	(17.3)	6.4
Kamalapur, Bangladesh; urban; 2008 (Brooks and colleagues, unpublished)***	Defined population base (n=4547)	History of cough with or without documented fever (axillary temperature - ≥ 38°C), WHO specified age specific elevated respiratory rate (0 - <2 months of age RR = ≥60/min, 2 - <12 months of age RR ≥ 50/min and 12 - <60 months of age RR ≥40/min) and chest wall indrawing	71.7	24
Multicentre, Bangladesh; rural; 2008 (Azziz-Baumgartner and colleagues, unpublished)	Defined population base (n=6864)	Cough or difficult breathing with chest wall indrawing or requiring hospitalization	51.3	14
Western Pacific				
Alabang (Metro Manila), Philippines; urban; 1985 -1987 (Tupasi et al., 1990)	Defined population base (n=709)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(64.8)	24
Western Australia, Australia; mixed rural-urban; 1988-1993 (Williams et al., 1997)	Census-derived estimate (n=757610)	Physician diagnosed ALRI	32.1	10.2
Zhejiang, China; mixed rural-urban; 1990-1991 (Sun et al., 1992)	Defined population base (n=7472)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	25	8.6
Zhejiang, China; rural; 1990-1991 (Hu and Lu, 1996)	Defined population base (n=1215)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(26.7)	9.9
Heilongjiang, China; rural; 1991–1993 (Wang et al., 1997)	Census-derived estimate (n=9901)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(137.3)	50.8
Shangdong, China; mixed rural-urban; 1992-1993 (Liu et al., 1994)	Defined population base (n=16751)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(5.5)	2
Chongqing, China; mixed rural-urban; 1992-1993 (Xie et al., 1993)	Census-derived estimate (n=2246)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	69.5	31.2
Heilongjiang, China; rural; 1993(Lou et al., 1995)	Census-derived estimate (n=5812)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(17.2)	6.4
Auckland, New Zealand; urban; 1993-1996 (Grant et al., 1998)	Census-derived estimate (n=50280)	Physician diagnosed ALRI	(24.2)	10.9

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
Fujian, China; rural; 1994 – 1995 (Chi et al., 1996)	Census-derived estimate (n=9323)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(65.5)	24.2
Henan, China; rural; 1994 (Chen et al., 1997)	Defined population base (n=7917)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	52.1	23.2
Jiangsu, China; rural; 1994-1995 (Chen, 1996)	Census-derived estimate (n=11729)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	33.8	9.4
Henan, China; rural; 1994-1996 (Mo, 1998)	Census-derived estimate (n=29590)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(128.1)	47.4
Fujian, China; mixed rural-urban; 1994-1995 (Huang et al., 1999)	Census-derived estimate (n=4665)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	52.5	24
Yunnan, China; rural; 1995-1997 (Xu et al., 2000)	Census-derived estimate (n=6966)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(529.2)	195.9
Shandong, China; mixed rural-urban; 1995-2001 (Gao et al., 2004)	Census-derived estimate (n=375629)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(41.9)	15.5
Shangdong, China; mixed rural-urban; 1995 – 2004 (Qu et al., 2009)	Census-derived estimate (n=537734)	Cough and / or difficult breathing with or without tachypnea AND chest wall indrawing	(34.8)	12.9
Western Australia, Australia; mixed rural-urban; 1996-2005 (Moore et al., 2010)	Census-derived estimate (n=911520)	Physician diagnosed ALRI (Discharge diagnosis- ICD-10 codes J12-J18, B59, B05.2, B37.1, B01.2)	52	20.9
Taiwan; 1997-2004 (Wu et al., 2009) †††	Census-derived estimate	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM codes 480-487)	49.8	39.7
Bohol, Philippines; mixed rural-urban; 2000-2004 (Lucero and colleagues, unpublished)§	Defined population base (n=6094)	Cough or difficulty breathing with chest wall indrawing	89.7	(33.2)
Tongatapu, Tonga; mixed rural-urban; 2000-2004 (Russell et al., 2009) §^	Census-derived estimate	Physician diagnosed ALRI	(27.2)	10.1
Hong Kong, urban; 2000-2005 (Ho et al., 2007)	Census-derived estimate (n=2131182)	Physician diagnosed ALRI (Discharge diagnosis- ICD-9 CM codes 481 and 486)	(19.1)	8.6

††† Excluded pneumonia in children aged 0-3 days

Location; population characteristic; study period (reference)	Study population (n)	Case definition	Incidence of hospitalised ALRI * (per 1000 children per year) †	
			0-11 months	0-59 months
Suva, Fiji; urban; 2001-2002 (Magree et al., 2005) §	Census-derived estimate (n=20954)	Physician diagnosed ALRI	(40)	18
NhaTrang district, Vietnam; mixed rural-urban; 2005-2006 (Anh et al., 2009)	Census-derived estimate (n=24641)	Physician diagnosed ALRI	69.5	22.6
Tongatapu, Tonga; mixed rural-urban; 2006 – 2007 (Russell et al., 2009) §	Census-derived estimate (n=10322)	Physician diagnosed ALRI	(19.5)	7.2
NhaTrang city, Vietnam; urban; 2007–2008 (Yoshida et al., 2010)	Census-derived estimate (n=13941)	Physician diagnosed ALRI	65.8	34

Table 10: Incidence and number of new episodes of hospitalised ALRI in young children aged below 5 years in 2008, by WHO region

	Age 0-11 months			Age 0-59 months		
Region	Number of studies ‡‡‡	Incidence (95% CI) §§§	Number of episodes (thousands) ****	Number of studies‡‡‡	Incidence (95% CI)§§§	Number of episodes (thousands)****
Africa	13 (2)	49.3 (30.4 to 79.8)	1343 (829 to 2174)	13 (3)	21.1(13.6 to 32.8)	2707 (1742 to 4206)
Americas	18 (1)	38.7 (30.0 to 50.0)	601 (466 to 777)	18 (6)	17.4 (12.0 to 25.3)	1361 (95% CI 939 to 1974)
Eastern Mediterranean	2 (0)	27.9 (14, 55.5)	432 (217 to 860)	2 (0)	12.1 (8.6 to 17.2)	894 (631 to 1266)
Europe	14 (9)	14.2 (8.1, 25)	157 (90 to 277)	14 (4)	7.3 (4.6 to 11.6)	383 (240 to 611)
South East Asia	13 (6)	49.8 (33.6 to 73.8)	1815 (1225 to 2688)	13 (4)	18.6 (11.4 to 30.3)	3355 (2057 to 5474)
Western Pacific	25 (15)	43 (32.3, 57.3)	984 (739 to 1310)	25 (1)	17.3 (13.4 to 22.3)	1973 (1529 to 2545)
Developing countries	61 (22)	48.6 (41.0 to 57.6)	5690 (4797 to 6750)	61 (12)	18.9 (15.9 to 22.4)	10764 (9063 to 12792)
Industrialised countries	24 (11)	19.1 (15.7 to 23.4)	221 (181 to 270)	24 (6)	9.6 (7.1 to 13.0)	543 (402 to 735)
Global ††††	85 (33)		5911 (4978 to 7020)	85 (18)		11309 (9465 to 13527)

‡‡‡ Data in parentheses indicate number of studies with imputed data

§§§ Data are incidence meta-estimates from random effects model; incidence estimates are per 1000 children per year

**** Data in parentheses are 95% CIs

†††† Number of new cases globally in the year 2008 is the sum of new cases in children residing in developing and industrialised countries; data in parentheses are 95% CIs

3.1.2.3. Number of hospitalised influenza-associated ALRI cases in 2008

3.1.2.3.1. Methods

The regional meta-estimates of the proportion of hospitalised ALRI cases positive for seasonal influenza (section 3.1.2.1.2) were applied to the regional estimates of (all-cause) hospitalised ALRI for the year 2008 that was estimated as described in section 3.1.2.2.2.

3.1.2.3.2. Results

Using the prevalence based approach, it is estimated that about 772,000 (95% CI 343,000 to 1.8 million) hospitalisations due to influenza-associated ALRI occurred worldwide in young children (0-59 months) in 2008 (Table 8). South-East Asia and Western Pacific region of the WHO accounted for 68% of this global "burden". The global estimates (772 (95% CI 343 to 1821) thousand) as well as the regional estimates (except for Americas and Europe) are consistent with the estimates obtained using the incidence-based approach (911 (95% CI 617 to 1356) thousand) (Table 12).

Table 11: Estimated number of hospitalisations due to influenza-associated ALRI in young children (0-59 months) in 2008 using a prevalence-based approach

Region	Proportion (%) of hospitalised ALRI positive for seasonal influenza (95% CI)	Estimated number of episodes of hospitalised ALRI in 2008 (thousands) *	Estimated number of seasonal influenza-associated hospitalised ALRI in 2008 (thousands)*
Africa	5.2 (2.4 to 11.1)	2707 (1742 to 4206)	141 (42 to 469)
Americas	3.6 (2.6 to 4.9)	1361 (939 to 1974)	49 (25 to 97)
Eastern Mediterranean	2.1 (0.9 to 5.0)	894 (631 to 1266)	19 (6 to 64)
Europe	8.4 (4.2 to 16.7)	383 (240 to 611)	32 (10 to 102)
South-East Asia	9.1 (6.8 to 12.3)	3355 (2057 to 5474)	306 (139 to 673)
Western Pacific	11.4 (7.9 to 16.3)	1973 (1529 to 2545)	225 (122 to 416)
Global †			**772 (343 to 1821)**

* Data in parentheses are 95% CIs

† Number of new cases globally in the year 2008 is the sum of new cases in children residing in the six WHO regions; data in parentheses are 95% CIs

Table 12: Comparison of the estimated number of hospitalisations due to influenza-associated ALRI in young children aged below 5 years in 2008 using the incidence and prevalence-based approaches

Region	Estimated number of hospitalisations due to seasonal influenza-associated ALRI in 2008 using prevalence–based approach (thousands) *	Estimated number of hospitalisations due to seasonal influenza-associated ALRI in 2008 using incidence–based approach (thousands)*
Africa	141 (42 to 469)	134 (113, 159)
Americas	49 (25 to 97)	95 (73, 126)
Eastern Mediterranean	19 (6 to 64)	NA †
Europe	32 (10 to 102)	55 (37, 82)
South-East Asia	306 (139 to 673)	257 (65, 1020)
Western Pacific	225 (122 to 416)	255 (105, 620)
Global	**772 (343 to 1821)**	**911 (617, 1356)**

* Data in parentheses are 95% CIs

† NA- Data not available

3.2. Influenza-associated ALRI mortality in 2008

3.2.1. Method

There are no global / regional estimates of the mortality attributable to seasonal influenza-associated ALRI in young children (0-59 months). Various modelling approaches have been used previously to estimate seasonal influenza-associated mortality (Simonsen et al., 1998, Simonsen et al., 2005, Thompson et al., 2003, Wong et al., 2004). These are described in detail in section 1.4. In order to precisely estimate the deaths due to influenza-associated ALRI in young children, two different data are required: good quality mortality data from vital registration / verbal autopsy studies; and good quality year round virological surveillance data for seasonal influenza and RSV as in many settings both viruses are known to co-circulate during the influenza season. Various studies have shown that the majority of ALRI deaths in developing countries occur at home, and vital registration data are incomplete (Adazu et al., 2005, Sacarlal et al., 2009, Sutanto et al., 2002, Rudan et al., 2005). Since data related to influenza-associated ALRI deaths were scarce, therefore modelling a point estimate for influenza-associated ALRI mortality was not attempted. Instead two approaches were used to assess the likely upper and lower boundary of ALRI mortality that could plausibly be attributed to influenza.

3.2.1.1. Approach 1 (hospitalised cases)

Studies reporting in-hospital case fatality ratio (CFR) for influenza-associated ALRI in hospitalised cases were identified from literature review and from unpublished data available with the Influenza Study Group. A meta-analysis of the in-hospital CFR was conducted using the random effects model to account for between-study heterogeneity. The pooled estimates and 95% confidence intervals were reported for industrialised and developing countries. These in-hospital CFR meta-estimates of influenza-associated ALRI were applied to the number of new cases of hospitalised influenza-associated ALRI (calculated individually for developing and industrialised countries) for the year 2008. Since access to hospital care in most developing countries is typically limited, it would be fair to assume that this result represents a lower bound for influenza-associated ALRI mortality.

3.2.1.2. Approach 2 (all cases)

The second approach was similar to the method used to estimate mortality due to RSV-associated ALRI in children (Nair et al., 2010). First, the definition for influenza season provided by Izurieta and colleagues was modified for tropical / subtropical settings as data on

influenza positivity were only available by month (Izurieta et al., 2000). Any month in which at least 10 samples were analysed, and influenza virus was detected in more than 5% of specimens was considered to be within the "influenza season". It was assumed that all excess mortality due to ALRI in children younger than 5 years during the "influenza season" was due to seasonal influenza virus, and that non-influenza mortality is equal within and between influenza epidemic periods. Since this approach represents an extreme case scenario, it was assumed that this method yielded an upper bound for influenza-associated ALRI mortality. The duration (in months) of the "influenza season" for each calendar year of the study (MonFLU) was defined. For each year, the average number of total ALRI deaths in the community that occurred per month during (AvgFLU) and outside (AvgOTHER) the "influenza season", as well the total number of deaths (TOTAL) during the year was computed. The proportion of yearly deaths due to influenza was then calculated as:

$$\frac{(\text{AvgFLU} - \text{AvgOTHER}) \times \text{MonFLU}}{\text{TOTAL}}$$

Population-based data to define "influenza season" and monthly death records (with cause of death attribution based on verbal autopsy data) from the same population for a period of three years were available from Ballabgarh, Haryana in India and Nairobi, Kenya (Nongkynrih et al., 2003, Ye et al., 2009). However, the Kenyan data were not suitable for this analytic approach as influenza virus was circulating throughout the years 2003-05 making it impossible to clearly delineate an "influenza season" (Figure 16). Application of this approach to the estimated mortality of children younger than 5 years due to ALRI in India in 2008 (Black et al., 2010) provided an estimate of all ALRI deaths attributable to influenza if community-based case ascertainment (to identify all severe cases of influenza-associated ALRI) was used. The ratio of influenza-associated ALRI deaths (using this approach) compared to the influenza-associated ALRI deaths in hospitalised cases (using the first approach) in India was then applied to the lower bound of influenza-associated ALRI mortality in developing countries to estimate the upper bound of global ALRI mortality attributable to influenza in children younger than 5 years.

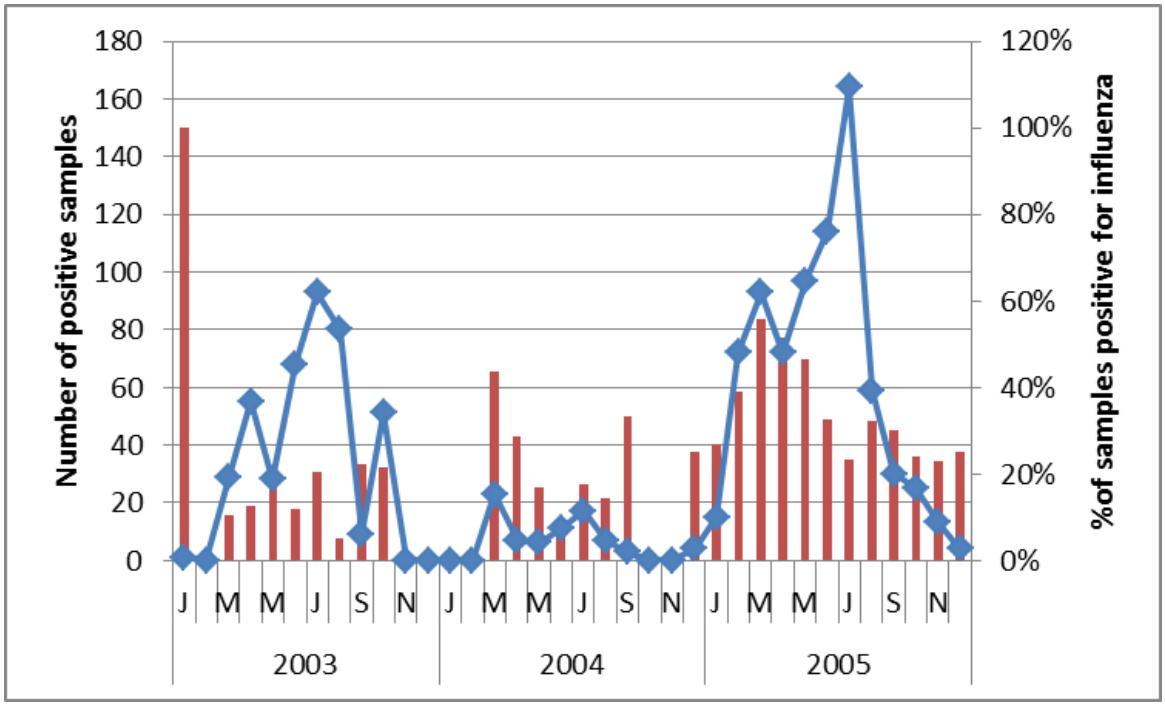

Figure 16: Seasonal pattern of laboratory confirmed influenza activity in Nairobi, Kenya from 2003 to 2005. The number of influenza positive samples is indicated using a blue line and the proportion (%) of samples positive for influenza is indicated using red bars. The continuous circulation of the influenza virus in 2005 made it difficult to delineate an influenza season

3.2.2. Results

3.2.2.1. Approach 1 (In-hospital mortality due to influenza-associated ALRI)

Twelve published and 8 unpublished studies providing in-hospital CFR data for deaths in children (aged 0-59 months) with influenza-associated ALRI admitted to hospital were identified (Figure 5). Eleven studies reported in-hospital CFR data from developing countries (Table 10). The data from developing countries demonstrated some heterogeneity (I^2 for heterogeneity=46.5%). However, there was no heterogeneity in the in-hospital CFR data from 8 studies in industrialised countries (I^2 for heterogeneity=0%). The in-hospital CFR meta-estimate for developing countries was roughly 8 times that for industrialised countries.

Table 13: In-hospital case fatality ratio in children aged below 5 years with an admission diagnosis of ALRI and positive for seasonal influenza

Location (Reference)	Study period	Case fatality ratio (%) for influenza-associated ALRI (n)
Developing countries		
Paraná State, Brazil (Coelho et al., 2007)	1996-2001	6. 7 (3/45)
Hong Kong (Nelson et al., 2007)	1997-1999	0.1 (7/5471)
Soweto, South Africa (Madhi and colleagues, unpublished)	1998-2004	5.6 (10/178)
Bohol, Philippines (Lucero and colleagues, unpublished) [*] [†] [‡]	2000-2004	7.5 (3/40)
Kuala Lumpur, Malaysia (Sam et al., 2010)	2002-2007	2.6 (3/116)
Hong Kong SAR, China (Kwong et al., 2009)	2005	1.2 (1/86)
Sa Kaeo and Nakhon Phanom, Thailand (Simmerman and colleagues, unpublished)	2005-2008	0.2 (1/430)
Kilifi, Kenya (Berkley and colleagues, unpublished)	2007	2.4 (1/41)
Bondo district, Kenya (Ope and colleagues, unpublished)	2007-2009	4.5 (3/67)
SARI Sentinel sites, Jordan, Oman, Egypt (Dueger and colleagues, unpublished)	2008	2.5 (2/80)
Santa-Rosa, Guatemala (Lindblade and colleagues, unpublished) [§§]	2008	28.6 (2/7)
Takeo town, Cambodia (Vong and colleagues, unpublished)	2008	5 (1/20)
CFR meta-estimate (95% CI)[†]	***2.5 (0.7, 4.4)***	***p (for heterogeneity)= 0.04, I^2=46.5%***
Industrialised countries		
South Australia, Australia (D'Onise and Raupach, 2008)	1996-2006	0.6 (4/626)
Philadelphia (PA), USA (Coffin et al., 2007)	2000-2004	0.9 (5/573)
Leicester, United Kingdom (Nicholson et al., 2006) [**]	2001-2002	0 (0/33)
Gipuzoka, Spain (Montes et al., 2005)	2001-2004	0 (0/70)
Salt Lake County (UT), USA (Ampofo et al., 2006)	2001-2004	0.3 (1/325)
Sydney, Australia (Milne et al., 2004)[*]	2003	6.3 (1/16)

[*] CFR meta-estimates if this study were excluded- 2.75%

[†] CFR meta-estimates if Philippines and Guatemala study are excluded- 2.71%

[‡] This study was in children aged 0-23 months

[§] CFR meta-estimates if this study were excluded- 2.92%

[**] CFR meta-estimates if these studies were excluded- 0.3%

Location (Reference)	Study period	Case fatality ratio (%) for influenza-associated ALRI (n)
Canada (Moore et al., 2006)	2003-2004	0.2 (1/424)
Multicentre, United States (Dawood et al., 2010)	2003-2008	0.2 (7/2998)
CFR meta-estimate (95% CI) [††]	***0.3 (0.1, 0.4)***	***p (for heterogeneity)= 0.78, I^2=0%***

The in-hospital mortality due to influenza-associated ALRI was calculated using the estimated number of new cases of influenza-associated hospitalised ALRI in the year 2008 (Table 6) and the in-hospital CFRs from children admitted with severe disease reported in hospital-based studies calculated separately for developing and industrialised countries (Table 13). Using this approach, it is estimated that approximately 21532 (95% CI 3958 to 55702) young children (aged 0-59 months) died in hospitals in 2008 because of influenza-associated ALRI (Panel 5). Ninety nine percent of all in-hospital deaths occurred in developing countries. There were insufficient data to calculate in-hospital CFR estimates in children in smaller age categories than 0-59 months.

3.2.2.1.1. Proportional contribution of influenza to all-cause in-hospital ALRI mortality

To estimate the proportional contribution of influenza to all-cause in-hospital ALRI mortality, the overall in-hospital CFR in young children aged 0-59 months was estimated using data from 24 published studies and 10 unpublished studies (Figure 14). Thirty one studies were from developing countries and three were from industrialised countries.

[††] CFR meta-estimates are from random effects model. In case of industrialised countries CFR meta-estimates from random and fixed effects models were identical

Table 14: In-hospital case fatality ratios for ALRI in children than 5 years (n=34 studies)

Location (reference)	Study Period	Case fatality ratio (%) for hospitalised *ALRI* (n)
Africa		
Kassena-Nankana District, Ghana (Morris and colleagues, unpublished)	1990-1991	3.3 (1/30)
Soweto, South Africa (Madhi and colleagues, unpublished)	1998-2005	6.2 (170/2722)
Bondo district, Kenya (Tornheim et al., 2007)	2001-2003	11.0 (120/1088)
Kilifi District, Kenya (Moisi and colleagues, unpublished)	2002-2008	9.5 (481/5041)
Upper River Division and Central River Division, The Gambia (Zaman and colleagues, unpublished)	2002-2004	12.0 (17/142)
Manhiça district, Mozambique (Roca and colleagues, unpublished)	2004-2006	8.7 (46/526)
Bondo district, Kenya (Ope and colleagues, unpublished)	2007-2009	4.3 (42/985)
Lwak, Kisumu, Kenya (Breiman and colleagues, unpublished)	2008-2009	1.5 (7/453)
Kibera, Nairobi, Kenya (Breiman and colleagues, unpublished)	2008-2009	1.4 (4/285)
Upper River region, The Gambia (Mackenzie and colleagues, unpublished)	2008-2009	3.7 (33/898)
CFR meta-estimate (95% CI) [*]	***5.9 (4.4 to 7.8)***	

[*] Data are in-hospital CFR meta-estimates (%) from random effects model

Location (reference)	Study Period	Case fatality ratio (%) for hospitalised *ALRI* (n)
Americas		
USA (Grijalva et al., 2010)	1997-2004	0.2
Paysandú and Salto, Uruguay (Hortal and colleagues, unpublished)	2000-2004	0.3 (7/2137)
Goiânia, Brazil (Andrade and colleagues, unpublished)	2000-2001	1.1 (3/281)
Colorado, USA (Simoes and colleagues, unpublished)	2000-2008	0.6 (298/50469)
Concordia and Parana, Argentina (Ruvinsky and colleagues, unpublished)	2002-2005	1.1 (17/1601)
Pilar, Argentina (Gentile and colleagues, unpublished)	2003-2005	0.2 (2/856)
Goiânia, Brazil (Andrade and colleagues, unpublished)	2007-2009	0.3 (12/4388)
Santa Rosa, Guatemala (McCracken and colleagues, unpublished)	2007-2008	4.8 (9/187)
Multicentre, El Salvador (Clara and colleagues, unpublished)	2007	1.1 (741/69140)
CFR meta-estimate (95% CI)	***0.8 (0.5 to 1.6)***	
Eastern Mediterranean		
Sana'a, Yemen (Banajeh, 1998)	1991-1995	8.7 (221/2554)
Karachi, Pakistan (Owais et al., 2010)	2007-2008	3.7 (2/54)
CFR meta-estimate (95% CI)	***7.6 (4.1 to 13.9)***	

Location (reference)	Study Period	Case fatality ratio (%) for hospitalised *ALRI* (n)
Europe		
Spain (Monge and Gonzalez, 2001)	1995-1996	0.4 (64/15877)
South East Asia		
Matlab, Bangladesh (Zaman et al., 1997)	1988-1989	7.4 (2/27)
Lombok, Indonesia (Gessner and colleagues, unpublished)	1999-2002	11.0 (656/5942)
Mirzapur, Bangladesh (Arifeen and colleagues, unpublished)	2004-2008	2.2 (17/780)
Multihospital surveillance, Bangladesh (Naheed and colleagues, unpublished)	2004-2008	8.0 (543/6802)
Patan, Nepal(Williams et al., 2009)	2005-2006	2.2 (8/360)
Multicentre, India (Chandran and colleagues, unpublished)	2005-2007	0.3 (2/695)
Nakhon Phanom and Sa Kaeo provinces, Thailand (Baggett and colleagues, unpublished)	2006-2008	0.8 (122/14782)
Bangalore, India (Shah et al., 2009b)	2006	5.8 (56/967)
Kamalapur, Bangladesh (Brooks and colleagues, unpublished)	2008	0.9 (1/109)
CFR meta-estimate (95% CI)	***2.9 (1.5 to 5.5)***	
Western Pacific		
Bohol, Philppines (Lucero and colleagues, unpublished)	2000-2004	1.6 (12/736)

Location (reference)	Study Period	Case fatality ratio (%) for hospitalised *ALRI* (n)
NhaTrang district, Vietnam (Anh et al., 2009)	2005-2006	2.6 (21/794)
Suva, Fiji (Magree et al., 2005)	2001-2002	2.8 (7/248)
CFR meta-estimate (95% CI)	***2.3 (1.7 to 3.2)***	

CFR meta-estimate for Developing countries [†] ***I^2=99%***	**2.6 (1.8 to 3.9)%**	***P<0.0005,***
CFR meta-estimate for Industrialised countries [†] ***I^2=87.8%***	**0.5 (0.3 to 0.7)%**	***P=0.004,***

The in-hospital CFR in young children aged 0-59 months with hospitalised ALRI was about 2.6 (95% CI 1.8 to 3.9) percent in developing countries in 2008, with the highest CFRs being reported by studies from Africa (Table 14). By contrast, the estimated CFR in industrialised countries was 0.5 (95% CI 0.3 0.7) percent (Table 14). When the in-hospital CFR meta-estimates for the developing and industrialised regions were applied to the incidence meta-estimates for the respective regions, it was estimated that worldwide in 2008, ALRI resulted in about 283,000 (95% CI 164,000 to 504,000) in-hospital deaths in children younger than five years. Ninety-nine percent of these deaths occurred in developing countries.

Thus, about 7.6% (21532/282602) (95% CI 2.4 to 11.1) percent of all in-hospital ALRI deaths are attributable to influenza. It is well recognised that 54 to 90% of all ALRI deaths in under-five children in developing countries occur outside health facilities (Adazu et al., 2005, Sacarlal et al., 2009, Sutanto et al., 2002). Therefore, the estimated 21532 in-hospital deaths represent only a proportion of the overall ALRI mortality at attributable to influenza. At best, this (1.4% of the estimated overall all-cause ALRI mortality in under-five children – 1.6

[†] Data in parentheses are 95% CIs

(95% CI 1.1 to 1.9) million (Black et al., 2010)) can be considered to represent a plausible lower bound of influenza-associated ALRI mortality.

3.2.2.2. Approach 2 (Overall mortality due to influenza-associated ALRI)

This approach used cause of death data in children not admitted to hospital, assigned by verbal autopsy, and influenza virus isolations in the same population during the same period. Such cause of death data were available only from one site- Ballabgarh (Haryana) in India for a three year period from 2006-2008 (Nongkynrih et al., 2003). Influenza isolation data from a sample of the same population (all age groups) accessing outpatient services for ILIs were available from the All India Institute of Medical Sciences (AIIMS) run referral hospital at Ballabgarh (Figure 17).

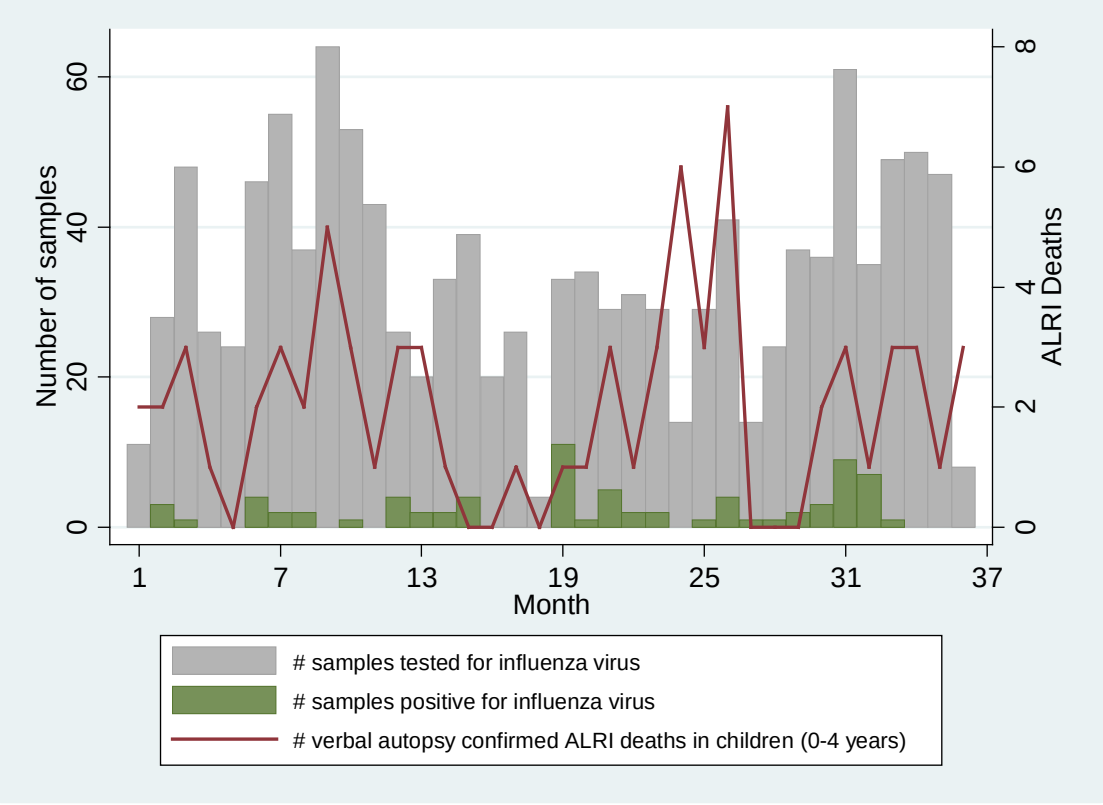

Figure 17: Pattern of verbal autopsy confirmed ALRI deaths in children younger than 5 years by circulation of influenza virus in the community in Ballabgarh, India (2006-08)

Month 1 corresponds to January 2006 and month 36 corresponds to December 2008

The ALRI deaths attributable to influenza (using mortality data in the community from verbal autopsy confirmed cause of deaths in Ballabgarh) – 24179 (as calculated in Table 15) was

applied to the published estimates of all-cause ALRI deaths in young children (0-59 months) in India in 2008 – 371605 (Black et al., 2010) Furthermore, the abovementioned estimated number of childhood ALRI deaths in India attributable to influenza (24179) was over 5 times higher than was estimated with approach 1 (step l, Panel 5). Available data from this site indicate that RSV circulated entirely outside the "influenza season" with no overlap (Broor, personal communication). Additionally the site has low malaria activity (AIIMS, 2010). If these data are assumed to be broadly representative of India, then 6.5% (24179/371605) of all paediatric ALRI deaths in India are associated with influenza from 2006-2008. If extrapolated to other developing countries, this approach yields a crude estimate (for developing countries) of approximately 114,450 (95% CI 21,000 to 300,000) deaths attributable to influenza-associated ALRI in young children in 2008 (Panel 5). Black and colleagues estimated that globally 1575257 ALRI deaths occurred in young children (0-59 months) in 2008 (Black et al., 2010). Therefore, the 114,450 influenza-associated ALRI deaths estimated above represents about 7.3% (114447/1575257) (95% CI 2.0 to 15.8) percent of overall all-cause ALRI mortality in young children. However, this method is likely to overestimate deaths because it assumes that all excess ALRI mortality during the "influenza season" is due to influenza. This assumption is not likely to be true, in view of other respiratory pathogens having a shared seasonality and the likelihood that influenza deaths occur outside the defined influenza season (especially in tropical and sub-tropical regions where the influenza virus circulates throughout the year) (Chiu et al., 2009, Sam et al., 2010). Additionally, this estimate is based on data from a single study in a small rural area in north India and is therefore unlikely to be generalizable. At best, this estimate can be considered to represent the plausible upper bound of mortality attributable to influenza-associated ALRI.

Table 15: Estimated influenza-associated ALRI deaths in India based on verbal autopsy confirmed ALRI deaths occurring in the community in children younger than 5 years in Ballabgarh, Haryana

	Duration of influenza season (in months)	Average no. of deaths per month during influenza season	Average no. of deaths per month outside influenza season	Total ALRI deaths per year	Proportion of ALRI deaths attributable to influenza	India influenza-associated ALRI deaths
2006	3	2.33	2.22	27	0.01	4588
2007	7	1.70	1.60	20	0.04	14864
2008	5	2.60	1.86	26	0.14	53086
Average influenza-associated ALRI deaths per year						24179

Approach 1: In-hospital case fatality ratios and incidence of influenza-associated hospitalised ALRI

Estimated new cases (in children younger than 5 years) of influenza-associated hospitalised ALRI in industrialised countries in 2008, a= 66685 (95% CI 50434 to 87419)

Estimated in-hospital case fatality ratio (CFR; for children younger than 5 years) due to influenza-associated ALRI yearly in industrialised countries, b= 0.27 (95% CI 0.10 to 0.44) %

Estimated in-hospital mortality due to influenza-associated ALRI in children (younger than 5 years) in industrialised countries in 2008, c= a x b= 180 (50 to 385)

Estimated new cases (in children younger than 5 years) of influenza-associated hospitalised ALRI in developing countries in 2008, d= 843952 (95% CI 566411 to 1268761)

Estimated in-hospital case fatality ratio (CFR; for children younger than 5 years) due to influenza-associated ALRI yearly in developing countries, e= 2.53 (95% CI 0.69 to 4.36) %

Estimated in-hospital mortality due to influenza-associated ALRI in children (younger than 5 years) in developing countries in 2008, f= d x e= 21352 (3908 to 55317)

Estimated global in-hospital mortality due to influenza-associated ALRI in children (younger than 5 years) in 2008, g= c + f= 21532 (95% CI 3958 to 55702)

Approach 2: ALRI mortality during influenza season based on data from Ballabgarh, India

Average proportion of ALRI mortality attributable to influenza during 3 years= 0.06

Estimated mortality due to ALRI in Indian children younger than 5 years= 371605 (Black et al., 2010)

Estimated mortality due to influenza-associated ALRI in children younger than 5 years, h= 24179 (mean of the three yearly estimates)

Estimated number of hospitalised cases of influenza-associated ALRI in children younger than 5 years in India in 2008 (applying the incidence of influenza-associated hospitalised ALRI in South-East Asia (Table 6) to under-five population in India in 2008), i= 178263

Estimated in-hospital mortality due to influenza-associated ALRI in Indian children, j= i x e= 4510

Proportion of mortality from this approach compared to approach 1, j=h / i= 5.36

Estimated global mortality due to influenza-associated ALRI (by extrapolating Indian model), k= j x f= 114447 (95% CI 20947 to 296450)

Panel 5: Estimated mortality due to influenza-associated ALRI in children younger than 5 years

In summary, insufficient data are available to make precise estimates of global mortality from influenza-associated ALRI. Two independent approaches with differing assumptions and limitations were adopted to obtain a rough data-derived estimate of the plausible lower and upper bound for influenza -associated ALRI mortality in young children. The estimates of mortality are consistent with influenza being associated with approximately 7% (uncertainty range 2 to 16%) of deaths from ALRI in children. Data from India and Kenya show substantial yearly variation in magnitude of influenza epidemic activity and associated ALRI deaths (Table 15, Figure 16, Figure 17). This finding suggests that national, regional and global influenza mortality could also vary widely from year to year.

Chapter 4. Influenza disease burden estimation using severe acute respiratory infection (SARI) Sentinel Surveillance data

4.1. Background

Although virological surveillance for influenza has been conducted through the global influenza surveillance network (GISN) over the last six decades, the data collected through the approximately 130 national influenza centres around the world are primarily aimed at monitoring changes in the antigenicity of influenza virus and guide the selection of strains for the annual influenza vaccine, rather than assessing severity of disease. This gap in epidemiological data became evident during the influenza pandemic of 2009. The lack of any established surveillance for severe disease in most countries and the resulting absence of historical data limited the ability of the WHO member states to evaluate the severity of the event in the context of previous seasons. Even where the data were available, they were not collected using a standardised approach, which meant that the data could not be interpreted outside the local context. Thus, the WHO suggested using standardised case definitions for influenza surveillance in 2010 and have now updated these with guidelines for influenza surveillance in WHO member states (WHO Global Influenza Programme, 2012). The "WHO interim global epidemiological surveillance standards for influenza" focuses on mild influenza like illness (ILIs) as well as on severe acute respiratory infections (SARI). One of the aims of the revised surveillance guidelines was to enable data collection for influenza disease burden estimation. The WHO issued a request for proposals (RFP) for developing a manual (aimed at low and middle-income countries) for estimating influenza disease burden in a population using locally available data using basic mathematical methods accessible to an individual with basic epidemiological training. A detailed proposal was prepared in response to this RFP and the project was awarded jointly to the author and his supervisor (Prof Harry Campbell).

4.2. Methods

Prior to the development of the final draft of the manual, the following preparatory activities were undertaken:

1. Needs assessment through survey of end-users in low and middle-income countries

2. Consultation with experts working in influenza disease burden estimation in low and middle-income countries
3. Engaging the services of an educational consultant for instructional design and content delivery
4. Engaging the services of a software developer for developing an electronic tool for disease burden estimation using the methods outlined in the manual
5. Selection of possible sites for a desktop pilot of the methods and tools outlined in the draft manual
6. Desktop pilot of the draft manual at three SARI surveillance sites in two developing countries
7. Undertaking appropriate revisions based on feedback from end-users, independent technical experts, and internal reviewers at the WHO (WHO Steering Committee).

4.2.1. Needs assessment

A questionnaire (Appendix A6) was developed by the author to consult end-users in developing countries in order to understand their perceived needs so as to appropriately inform the design and content of the manual. This questionnaire was circulated to influenza focal points in 40 low and middle-income countries through the Global Influenza Programme, WHO. Twenty seven end-users in 24 countries (24 respondents in developing and three in industrialised countries) responded to the survey (Table 16).

Table 16: Location of respondents to the end-user survey for informing design and content of the influenza disease burden manual

Africa	Americas	Eastern Mediterranean	Europe	South East Asia	Western Pacific
Algeria	Brazil	Morocco	Armenia	Sri Lanka (2 respondents)	Mongolia (2 respondents)
Cameroon	Cuba	Oman	Belarus		Singapore
Côte d'Ivoire	Mexico		Georgia		
Ethiopia			Israel		
Ghana			Kyrgyzstan		
Madagascar			Portugal		
Uganda (2 respondents)			Russia		
South Africa			Ukraine		

All respondents were MDs/ Ph.Ds/Masters in Public Health and working as epidemiologists in the Influenza Division in the Ministry of Health in the above countries. A majority of the respondents (48%) had ≥ 10 years' experience as an epidemiologist and 30% had experience ranging between 6 and 10 years. Almost all (93%) felt that seasonal influenza was an important public health problem in their country. The respondents were asked to indicate what, in their opinion, were the best data sources that could contribute to influenza disease burden estimation. Eighty one percent (22/27) of the respondents indicated that, in their opinion, population-based data from sentinel sites were the best data source that could contribute to influenza disease burden estimation. Other sources of data that were indicated as being useful for disease burden estimation were:

a. data on hospitalised children with ALRI positive for influenza where the denominator population (for the hospital catchment area) can be estimated using healthcare utilisation surveys- 59% (16/27)
b. data on hospitalised children with ALRI positive for influenza where the denominator population (for the hospital catchment area) cannot be estimated- 41% (11/27)

With regard to availability of influenza related data in their respective countries, 96% of the respondents indicated that they had data from sentinel surveillance for ILI/SARI (Table 17).

Exclusion of the three industrialised countries (Israel, Portugal and Singapore) from the analysis did not alter the results.

Table 17: Current availability of influenza-related data in the WHO member states responding to the survey (N=24 respondents)

Data source	Overall availability (n)	Availability in 21 developing countries (n)
Sentinel surveillance for ILI / SARI	96% (23)	95% (20)
Hospital surveillance for respiratory infections	67% (16)	66% (14)
Laboratory surveillance for influenza virus	54% (13)	48% (10)
ARI/pneumonia surveillance	29% (7)	19% (4)

The survey indicated that while 85% of the respondents routinely analysed and monitored the timeliness of reporting of influenza surveillance data, they were not using it appropriately for either improving influenza surveillance or for assessing influenza-associated morbidity (Table 18).

Table 18: Current patterns of action on influenza surveillance data in WHO member states (N=27 respondents)

Activity	Overall respondents utilizing data for the activity (n)	Developing country respondents utilizing data for the activity (n)
Analyse data and monitor timeliness of reporting	85% (23)	83% (20)
Update influenza surveillance database	59% (16)	58% (14)
Provide data to Ministry of Health	48% (13)	46% (11)
Assess influenza-associated morbidity	48% (13)	50% (12)
Alert unusual influenza activity	26% (7)	25% (6)
Estimate influenza seasonality	22% (6)	21% (5)
Improve influenza surveillance	22% (6)	21% (5)

The majority (63%) of respondents indicated that the main limiting factor for influenza disease burden estimation was the lack of relevant / reliable data on influenza cases (Table 19). About a third (37%) of the respondents indicated the lack of a clear denominator (population at risk) as another reason which did not permit disease burden estimation.

Table 19: Perceived gaps in the capacity to conduct disease burden estimation in the WHO member states (N=27 respondents)

Factor	Overall Response (n)	Response from respondents in developing countries (n)
Lack of reliable / relevant data on influenza cases	63% (17)	54% (13)
Shortage of trained manpower	44% (12)	46% (11)
Lack of denominator data	37% (10)	33% (8)
Lack of laboratory facilities and equipment	30% (8)	33% (8)
Lack of political commitment	26% (7)	29% (7)
Lack of a dedicated influenza section in Ministry of Health	15% (4)	17% (4)
Lack of awareness amongst policy makers	15% (4)	13% (3)

Overall 74% (20/27) of the respondents and 79% (19/24) of the respondents from developing countries thought it was essential / very useful in the context of their country to have a manual providing generic guidelines for influenza disease burden estimation.

> "We don't have any similar manual in our country. The burden estimate is needed to make decisions regarding organizing necessary organizational and prevention activities, and also to make a decision regarding the finances distribution in order to implement those activities."
>
> (Respondent from Eastern European country)

> "This manual will enable us to study on the socioeconomic impact of influenza in our country. This is an important incentive for the politician to get involved in influenza surveillance. For over a decade that we monitor flu we are not able to answer these questions. What is the burden of the flu? flu is it a major public health concern?"
>
> (Respondent from African country 1)

There was however, some concern that this may prove to be a double-edged sword especially if the estimated burden was lower than what is perceived generally.

> "It will give an idea of how important influenza is as a contributor to overall respiratory disease. My concern is that if it's not found to have a significant share in the overall disease burden (after

> reviewing several years systematically collected data), there will be less interest to continue with generating flu disease burden estimates."
>
> (Respondent from African country 2)

Only one respondent from an industrialised country felt that there was no need for a manual in their national context.

> "I not sure if a manual will be something that GP will read. There is too many paper work and formularies in order to make a manual for influenza a really instrument of work. Could be theoretically useful. Perhaps a small manual (more operative) with main boxes with resume of action in each chapter could be considered for practical use. The main challenge will be a manual that people will really read and put to practical! Guidelines are different concept from manual and people usually give more attention!"
>
> (Respondent from industrialised country)

Eighty nine percent (24/27) of the respondents (78% in developing countries) felt that the manual should be aimed at epidemiologists. Health care planners and decision makers were identified as another important target group for the manual (74% overall and 67% in developing countries). Although a spread sheet based model to assist in disease burden estimation was not part of the RFP and the approved project proposal, the author felt that this would be a useful adjunct to the manual in low and middle income countries where users have limited access to statistical packages. Ninety six percent (26/27) of the respondents overall (identical proportion from developing countries) affirmed this proposal.

> "Yes, it could be more useful than a complete and meticulous manual with a lot of guidelines and complex methods difficult to understand and follow."
>
> (Respondent from Latin American Country)

4.2.1.1. Expected outcomes

The respondents had varied expectations of the manual. While the majority felt that the manual would assist in implementation of SARI sentinel surveillance, a few of the respondents expected the manual to:

- improve case reporting
- assist in assessing the economic impact of influenza
- improve surveillance in order to have quality data
- provide guidance on how to interpret and communicate results

The respondents were provided with the proposed content for the manual and were asked to indicate how useful this would be in their local context (Table 20). They were also requested to provide some any additional content which was likely to be useful. Eighty-nine percent (24/27) of the respondents felt that the proposed table of contents was useful in their individual countries settings. Specifically, the majority of the respondents felt that the chapters on data management; use of simple mathematical methods to estimate disease burden; standardisation of case definitions; and use of healthcare utilisation surveys to supplement available data were the highlights of the manual. Some of the respondents were of the opinion that the chapter on communicating data should include a section on communicating results to the general public. One respondent felt that the manual should detail the procedure for setting up a national surveillance system. Three proposed content items: namely using other data sources to check the plausibility of the estimates; data-sharing with neighbouring countries; and taking action to promote local ownership of the data scored low on the priority list of the respondents (less than 50% of the respondents considered these to be essential). None of the respondents felt that any of the proposed content was not relevant for inclusion in the manual.

Table 20: Results of the survey regarding proposed content for the manual

Content	Overall response * (n=27)			Response excluding industrialised countries* (n=24)		
	Essential	Useful to include	Uncertain	Essential	Useful to include	Uncertain
Background	63 (17)	30 (8)	7 (2)	71 (17)	21 (5)	8 (2)
Rationale and need for influenza burden estimate	78 (21)	19 (5)	4 (1)	79 (19)	17 (4)	4 (1)
Meaning of disease burden (definitions and descriptions of various ways to describe burden)	93 (25)	7 (2)	0 (0)	100 (24)	0 (0)	0 (0)
Description of target audience	44 (12)	41 (11)	15 (4)	46 (11)	38 (9)	17 (4)
Identifying the various sources of data for influenza	74 (20)	26 (7)	0 (0)	79 (19)	21 (5)	0 (0)
Critical review of data for quality and relevance	74 (20)	26 (7)	0 (0)	83 (20)	17 (4)	0 (0)
Selecting appropriate data sources	85 (23)	15 (4)	0 (0)	88 (21)	13 (3)	0 (0)
Mapping case definitions / data to appropriate ICD codes to aid interpretation of data	59 (16)	37 (10)	4 (1)	63 (15)	33 (8)	4 (1)
Adjusting for incomplete data (accounting for sampling variation)	59 (16)	37 (10)	4 (1)	58 (14)	38 (9)	4 (1)
Utilizing data from health utilization surveys to improve burden estimates	59 (16)	30 (8)	11 (3)	58 (14)	29 (7)	13 (3)
Adjusting for incomplete data on denominator	74 (20)	22 (6)	4 (1)	75 (18)	21 (5)	4 (1)

* Data are proportion (%) of respondents; data in parentheses indicate actual numbers

Content	Overall response * (n=27)			Response excluding industrialised countries* (n=24)		
	Essential	Useful to include	Uncertain	Essential	Useful to include	Uncertain
population						
Estimating incidence, number of new episodes and mortality range in a calendar year	81 (22)	19 (5)	0 (0)	83 (20)	17 (4)	0 (0)
Delineating influenza season	56 (15)	44 (12)	0 (0)	58 (14)	42 (10)	0 (0)
Expressing a confidence range for estimates	63 (17)	33 (9)	4 (1)	63 (15)	33 (8)	4 (1)
Carrying out a plausibility check with other available data	37 (10)	56 (15)	7 (2)	38 (9)	54 (13)	8 (2)
Looking at time trends over the years	63 (17)	37 (10)	0 (0)	67 (16)	33 (8)	0 (0)
Presenting the data in an appropriate format for local decision makers	73 (19)	23 (6)	4 (1)	79 (19)	17 (4)	4 (1)
Considering strategies to make appropriate use of these data in health services planning and priority setting	63 (17)	37 (10)	0 (0)	71 (17)	29 (7)	0 (0)
Taking actions to promote local ownership of these data	37 (10)	48 (13)	15 (4)	42 (10)	46 (11)	13 (3)
Encouraging data sharing with neighbouring countries to compare influenza burden	37 (10)	48 (13)	15 (4)	42 (10)	46 (11)	13 (3)
How seasonal patterns of influenza relate to seasonal patterns in ALRI hospital admission and how to interpret these findings	74 (20)	22 (6)	4 (1)	75 (18)	21 (5)	4 (1)

4.2.2. Technical advisory panel (TAP)

A technical advisory panel of six international experts who are familiar with influenza surveillance data and disease burden estimation studies in low and middle-income countries was constituted. These experts included representatives from United States Centres for Disease Control and Prevention (US CDC); the Afriflu Alliance, which has been strengthening influenza surveillance in sub-Saharan Africa (Steffen et al., 2011); the WHO; and health professionals from low and middle-income country sites with relevant local influenza data. The TAP met in Edinburgh on May 26, 2011 under the chairpersonship of the author and Prof Harry Campbell and discussed the availability of data, possible approaches to data assembly, data interpretation and disease burden estimation based on the nature of the target audience and their requirements. The following were the main decisions agreed upon in the meeting:

- The manual is not meant to contribute to global influenza burden estimation directly but rather give countries tools to better understand data and produce their own estimates; and appreciate the importance of influenza in relation to other health problems.
- The manual should be structured like an "instructional cookbook" giving guidance on what can be done with available data (explain with examples).
- The manual should be targeted at those with basic epidemiological training; and the output should be focused on those in the Ministry of Health (MOH).
- A simple spread sheet-based model which will allow countries to calculate national disease burden estimates should accompany the manual.
- The manual should guide the end-user on how to interpret data and present results to policy makers. This should include a discussion on limitations of these data and caution not to over-interpret data.

4.2.3. External educational consultant

The majority of the respondents of the initial survey were of the view that while the proposed content of the manual was comprehensive, it would be challenging to summarise all the information in a user-friendly manner in a single manual.

> "The content is sufficient and well organized. The advice will be to be concise during the writing process and avoid long paragraph."
>
> (Respondent from South East Asian Country)

Therefore, Agence de Médicine Préventive (AMP), an educational consultancy with proven technical expertise and experience in development of learning materials and tools was engaged to assist with instructional design and content delivery. While the technical content would be provided by the author, AMP were required to help clarify goals and objectives of the manual, advise on the instructional design, help develop some activities (including assessments) within the manual, assist in the editing of the final text for clarity and coherence and produce a ready-for-publication master copy.

4.2.4. External software developer

MDigital, a software developer was sub-contracted the task of developing the electronic tool (spread sheet based model) based on the methods outlined in the manual. They were required to work in co-ordination with the author.

4.2.5. Selection of developing country sites for desktop pilot of the manual

It was decided that the manual should be desktop piloted [†] in at least two developing country sites with good quality SARI surveillance-preferably one in Africa and another in Asia. The choice of the countries would depend on the type of surveillance sites (i.e. nested within a demographic surveillance site (DSS) / or secondary hospital with a known catchment area / or secondary or tertiary care facility where a catchment area cannot be defined); availability of data (sites with year-round surveillance with data for at least a couple of years); working language (desktop pilot was to be restricted to Anglophone countries); and an expression of interest by member states to participate in this exercise. Eight nine percent (24/27) of the respondents to the initial survey were enthusiastic regarding participation in the desktop pilot of the draft manual. After extensive consultation with experts at the WHO, India and Ghana were selected as the sites for desktop pilot of the manual. One technical expert (leading influenza work) from each of these countries was invited to be part of the TAP. After informal consultations with these experts during the TAP Meeting, a formal request for the desktop pilot was sent to the Ministry of Health in Ghana and the National Institute of Virology in India.

[†] Desktop pilot is defined as testing the methods and tools outlined in the manual using retrospective data at a field site

In the case of India, two sites (nested within a DSS), which were part of the US CDC funded Influenza Disease Burden India (IDBI) project were selected for the desktop pilot. Both sites had different characteristics. While one site (Ballabgarh) had been operational as a field practice area for a large teaching hospital (All India Institute of Medical Sciences) in New Delhi for over 40 years and had a number of large healthcare facilities within a 10 km radius, the other site (Vadu) was only 10 years old and was a relatively remote rural site with the sentinel site being the only nearby healthcare facility for the denominator population. The Ballabgarh site additionally had outpatient facilities where influenza like illness (ILI) surveillance was conducted. It was decided that the desktop pilot would be conducted on-site rather than at a central location in India.

In the case of Ghana, there were four SARI sentinel sites. Three of the four sites were such that a catchment area could be defined. The fourth site was a tertiary care centre in the capital city, Accra, where the patients from across the country sought healthcare. The desktop pilot was to be conducted at a central location in Accra.

For the desktop pilot at both locations a common format was followed. The two-day desktop pilot at both locations was led by the author was accompanied by an expert from the WHO. After the introductory talks outlining the context for the manual and how the manual was structured, the participants were required to read the manual (although a copy of the manual had been shared in advance with the participants). Each chapter was then discussed in detail and feedback was provided to the author. Thereafter, on the second day of the workshop, the participants were introduced to the electronic tool (spread sheet model). A general talk by the author was followed by an introductory video demonstration prepared by the external software developers. The participants then tested the electronic tool using their own data and identified operational issues with the model.

4.3. Results

4.3.1. The manual

Based on the feedback from the prospective users of the manual and the recommendations by the experts in the TAP, a "Draft Manual for Estimating Disease Burden associated with Seasonal Influenza in a Population" was prepared. The manual was prepared using a bottom-up approach i.e. the manual is mainly focused on an end-user based at a sentinel site rather than an epidemiologist at the national level. After the introductory chapters outlining the key concepts in influenza disease burden estimation, the users are provided with a detailed chapter on identifying and selecting data sources. This chapter provides the users with detailed concepts relating to reviewing their data for quality and relevance using the parameters of completeness, representativeness, accuracy, and bias. At the end of each concept, the users are provided with worked examples and are then required to review their own data using the checklist provided in the appendix. The subsequent sections on disease burden estimation are structured according to the three different data sources- SARI sentinel site; hospital not designated as a SARI sentinel site; and ILI sentinel site.

The chapter on SARI sentinel sites provides users with guidelines on adjusting case counts when clinical specimens are collected in only a proportion of eligible SARI cases. Since the majority of SARI sentinel sites are secondary care facilities where the denominator population is not known *a priori*, but can be estimated with some effort, this chapter provides detailed guidelines on estimating the catchment population. Previously, the US CDC have used healthcare utilisation surveys (HUS) for estimating the denominator population for a sentinel site. HUS though robust, are resource intensive and not very straightforward (Lindblade et al., 2011, Breiman et al., 2011, Jordan et al., 2009, Clara et al., 2012, Azziz-Baumgartner et al., 2012). Therefore, in this manual, the author has proposed an alternative method (Hospital Admission Survey) for estimating the denominator population using an administrative review of the inpatient records of the various healthcare facilities in the catchment area of the SARI sentinel site. In this method, the catchment area of the SARI sentinel site is assumed to be the lowest (i.e. most peripheral) administrative unit (in which the sentinel site is located), for which population data are available. Once the proportion of pneumonia cases seeking care at the sentinel site has been estimated after reviewing hospital admission records (at all likely points of care) for the past 3 to 5 years, this can be applied to the population of the lowest administrative unit, to estimate the catchment population of the SARI sentinel site. Identification of the catchment population by age group and gender would

enable the sentinel site to estimate the gender and / or age -specific incidence rate due to influenza-associated SARI. In the scenario where the denominator population cannot be estimated (e.g. tertiary care centres catering to patients from all over the country / large teaching hospitals), the chapter provides guidelines on estimating the disease burden associated with seasonal influenza by estimating the proportion of SARI cases positive for seasonal influenza.

The other chapters provide guidance on estimating disease burden using data from hospitals not designated as SARI sentinel sites (and therefore requiring mapping the case definition/ICD code to the SARI case definition); estimating disease burden in specific risk groups; and estimating disease burden using ILI sentinel surveillance data. One chapter on estimating disease burden using data from multiple sentinel sites is aimed solely at epidemiologists working at the national level. The manual concludes with detailed guidance on interpreting the results and key aspects to bear in mind when communicating findings to the appropriate audience (policymakers/health professionals/general public/surveillance sites).

4.3.2. Desktop pilot

The draft manual was reviewed by the Steering Group at the WHO and the independent panel of experts (TAP) in October and November 2011. The experts provided detailed comments for consideration by the author. Based on their feedback, a revised version was prepared for the desktop pilot. The desktop pilot of the manual was conducted at two sites (Ballabgarh and Vadu) in India and at one site (Accra) in Ghana in December, 2011 and January 2012 respectively. The participants were varied in terms of their background and experience in influenza surveillance. Overall, 18 participants (10 in India and 8 in Ghana) participated in this exercise. Twelve of the participants were epidemiologists and six were data analysts or program managers. While four of the participants were senior epidemiologists (more than 10 years of experience), four were relatively new to influenza surveillance. This diversity was important as the manual was targeted at professional audiences (with similar abilities and experience).

At the end of the desktop pilot, the participants were asked to provide feedback on a structured questionnaire (and score each question on a scale of 0 to 5 with 5 being consistent with complete agreement). The feedback has been summarised in Table 21. Overall, the participants expressed satisfaction with the content and delivery of the manual. The feedback

from all three sites was largely similar except that in Ballabgarh the participants examined the manual more critically than at the other two sites, which is reflected in the overall scores from this site. This is not surprising as the participants at Ballabgarh were MDs with a Master's degree in Public Health and were working at the premier medical school in India. Overall, all participants felt that the manual provided useful background information on essential epidemiological concepts for someone (with a minimal training in epidemiology) attempting to undertake influenza disease burden estimation.

> "With the training I have received in public health, this was essentially a repeat (concise one) of the training."
>
> (Participant from India trained in Public Health)

> "Good step-by-step approach. Was helpful"
>
> (Participant from India working as Data Analyst)

All participants felt that the manual was a good starting point for someone not previously trained in influenza disease burden estimation.

> "I have been involved in influenza disease burden related activities since last three years already and did not learn anything new from this manual. However, I do believe that people who haven't been as involved as I am would greatly benefit."
>
> (Participant from India working as Epidemiologist)

However, some of the participants felt that the manual was too detailed. They advised that inclusion of more pictures and flowcharts would make it less daunting for the reader.

> "I was overwhelmed in a positive sense. The information was good but with much repetition."
>
> (Participant from Ghana working as Data Analyst)

> "Pictures, more flowcharts and text boxes could be included"
>
> (Another participant from Ghana working as Epidemiologist)

Table 21: Feedback regarding the technical content and organization of the manual during the Desktop Pilot in India and Ghana (n=18 participants)

Question	Proportion (%) of participants in agreement (score)			
	Ballabgarh	**Vadu**	**India total**	**Ghana total**
Purpose/objectives				
The rationale and the global introduction to the manual were clear and easy to understand	78.3 (23.5)	100 (20)	87 (43.5)	92.5 (37)
The objectives of the manual were clearly stated	81.7 (24.5)	100 (20)	89 (44.5)	95 (38)
Technical content				
The technical content was consistent with the manual's objectives	81.7 (24.5)	95 (19)	87 (40.5)	97.5 (39)
The technical content extended your knowledge on what burden of disease is	73.3 (22)	90 (18)	80 (40)	95 (38)
The technical content extended your knowledge on how to estimate disease burden	73.3 (22)	90 (18)	80 (40)	100 (40)
More specifically, the technical content extended your knowledge on using your surveillance data for influenza cases	73.3 (22)	95 (19)	82 (41)	92.5 (37)
More specifically, the technical content extended your knowledge on assessing the quality of the numerator and denominator data	76.7 (23)	95 (19)	84 (42)	92.5 (37)

Question	Proportion (%) of participants in agreement (score)			
	Ballabgarh	**Vadu**	**India total**	**Ghana total**
More specifically, the technical content extended your knowledge on making any necessary adjustment to these data	70.0 (21)	90 (18)	78 (39)	92.5 (37)
More specifically, the technical content extended your knowledge on combining data from multiple sites	66.7 (20)	75 (15)	70 (35)	85 (34)
More specifically, the technical content extended your knowledge on how to estimate influenza disease burden at the national level	68.3 (20.5)	75 (15)	71 ((35.5)	95 (38)
The technical content could be easily applied in real-work situations	78.3 (23.5)	90 (18)	83 (41.5)	90 (36)
The language used in the manual to explain technical content was clear and easy to understand	83.3 (25)	100 (20)	90 (45)	95 (38)
Flow				
The content was organized in a manner that allowed each technical concept to build upon the previous one	83.3 (25)	95 (19)	88 (44)	90 (36)
Your attention was sustained throughout the manual	90.0 (27)	92.5 (18.5)	91 (45.5)	85 (34)
As a reader you don't feel overwhelmed by information	78.3 (23.5)	100 (20)	87 (43.5)	77.5 (31)
Content presentation and layout				

Question	Proportion (%) of participants in agreement (score)			
	Ballabgarh	**Vadu**	**India total**	**Ghana total**
The presentation of the technical content extended the learning experience	80 (24)	100 (20)	88 (44)	97.5 (39)
The layout of the manual supported the learning experience	83.3 (25)	95 (19)	88 (44)	90 (36)
Instructions on how to use the manual were clear and easy to understand	80 (24)	95 (19)	86 (43)	90 (36)
Information could be rapidly found within the manual	76.7 (23)	95 (19)	84 (42)	90 (36)
The page design, which includes text, fonts, icons and background, was visually pleasing	75 (22.5)	95 (19)	83 (41.5)	82.5 (33)

Based on this feedback, the manual was revised after extensive consultations with the instructional designers (AMP). Illustrations to explain new concepts were developed and a system of colour coding and symbols was used to segregate the sections and highlight important concepts respectively. The revised manual was sent again to the experts at WHO and the TAP members for their comments. All reviewers felt that the revised version was much improved and that their initial concerns had been addressed.

4.3.3. Spread sheet model

Following a video demonstration of the electronic tool, the participants were provided with a copy of the spread sheet model on their laptops and an instruction booklet. At all three sites, the participants utilised the second day of the workshop for familiarising themselves with the tool and using their influenza surveillance data to identify outstanding issues with the tool. Although there was not enough time for them to estimate disease burden associated with influenza at their sentinel site, they were able to input data for at least three months in each of the categories (SARI sentinel site with known population denominator, SARI sentinel site with an unknown population denominator, ILI sentinel site without a known population denominator). All participants found the tool to be extremely helpful and appreciated the accompanying video demonstration as an instructional tool.

> "This is a useful tool. Could be extended to other disease burden estimation aside from influenza."
>
> (Participant from Ghana)

They however expressed concerns regarding the ease of navigation between the different months within the tool.

> "The start screen can include navigation instructions."
>
> (Participant from India)

> "Cannot move between the months freely."
>
> (Participant from Ghana)

The general feedback from 17 participants (one participant from India did not attend the second day of the workshop) is summarised in Table 22.

Table 22: Feedback from seventeen participants during the desktop pilot of the spread sheet model in India and Ghana

Item	Proportion (%) of respondents (n)			
	Strongly Agree	Agree	Disagree	Strongly Disagree
Directions for navigating within the spread sheet model were clear and easy to understand	35.3 (6)	52.9 (9)	11.8 (2)	0 (0)
Instruction booklet on how to use the spread sheet model was clear and easy to understand	17.6 (3)	82.4 (14)	0 (0)	0 (0)
The video demonstration of the model was clear and easy to understand	29.4 (5)	64.7 (11)	0 (0)	5.9 (1)
The video demonstration is an useful adjunct to the instruction booklet	29.4 (5)	70.6 (12)	0 (0)	0 (0)
Selecting input options (based on type of data available) occurs easily within the spread sheet model	29.4 (5)	70.6 (12)	0 (0)	0 (0)
Calculating data occurs easily within the spread sheet model	52.9 (9)	47.1 (8)	0 (0)	0 (0)
Compiling data occurs easily within the spread sheet model	29.4 (5)	70.6 (12)	0 (0)	0 (0)
Getting required output for burden estimates occurs easily within the spread sheet model	35.3 (6)	64.7 (11)	0 (0)	0 (0)
This tool is a useful complementary tool of the manual	47.1 (8)	52.9 (9)	0 (0)	0 (0)

Based on the feedback from the participants, the spread sheet model was revised considerably. Specifically, navigation bars were added to make navigation from one month to another easy without having to return to the main screen and new graphical outputs were added. The beta version of the model (http://www.homepages.ed.ac.uk/eseodora/flu/index.php) was circulated amongst International Emerging Infections Program (IEIP) field sites of the US CDC and country offices of the WHO European Region to conduct further tests which would assist in identifying and fixing any bugs in the program.

4.3.4. Evaluation

The draft manual has been submitted to the WHO for official clearance (Appendix A9). Meanwhile, Eastern Mediterranean Regional Office of the WHO expressed an interest in undertaking influenza disease burden estimation in the member states in their region. To this end, the author was invited for a Consultation Meeting (15-17 May, 2012) to discuss the possibility of using this manual for the disease burden estimation. Apart from officers from the WHO, representatives from US CDC (NAMRU-III) and academics working on influenza surveillance participated in the meeting. After extensive discussions, the WHO Regional Office decided to adopt the manual. All participants agreed that influenza surveillance in the member states in the region was of variable quality and not all member states would be in a position to undertake disease burden estimation in the first instance. Rather, the most pragmatic approach would be to initiate this in those countries in the region that had good quality data for at least 12 consecutive months. In order to identify the member states most likely to have such data, the author was invited to present the manual and the spread sheet model to the member states at an Inter-Country Meeting from 27-29 August, 2012. The author outlined to the participants the minimum data requirements for undertaking disease burden estimation. Based on this, eight countries (namely Egypt, Iran, Jordan, Oman, Morocco, Pakistan, Palestine and Qatar) were identified for participation in a disease burden estimation workshop to be held in Egypt in December, 2012. All eight countries agreed to collect and prepare data for at least one sentinel site (in the format outlined in the manual) prior to the meeting.

The WHO Eastern Mediterranean Regional Office's decision to undertake influenza disease burden estimation is timely as there are hardly any data from this region. Even though the manual is being translated in Arabic, the implementation is likely to be very challenging

given the lack of trained epidemiologists and general civil unrest in the region. The workshop will assist in evaluating the implementation of the tools proposed in the manual in a variety of developing country settings.

Chapter 5. Discussion

This body of work estimates that about 1 million young children aged 0-59 months were hospitalised due to influenza-associated ALRI in 2008. It is also estimated that in the same year, about 22,000 to 115,000 deaths in children aged 0-59 could be attributable to influenza associated ALRI. This indicates that influenza contributes to about 8% of all hospitalised ALRI cases and about 7% of all ALRI deaths in children aged 0-59 months.

5.1. Strengths

This work included herein is the first to estimate the number of hospitalised influenza-associated ALRI cases and the mortality attributable to influenza-associated ALRI in children younger than five years. The author utilised different data sources and methods to triangulate the estimates and demonstrated that the estimates using different approaches are consistent with each other and with previously published ALRI estimates The main strength of the thesis lies in the use of extensive amounts of unpublished data (especially from developing countries) to supplement data from published literature. The author successfully established and led three large international collaborative groups (first the RSV Study Group, then the Influenza Study Group, and finally the Severe ALRI Working Group) each of which demonstrated progressive expansion in terms of numbers and representation of geographical sites. The members of these international consortia are leading experts in paediatric pneumonia and influenza. The author also established close working relationships with US CDC (a global leader in influenza research) and the WHO (policy-making body on influenza vaccines and research). The methods and tools developed by the author for estimating disease burden using SARI Sentinel surveillance data would be useful in providing disease burden information in high risk groups (e.g. pregnant women, young children, those with comorbidities etc.). Such information is vital for prioritising the use of vaccines in resource limited settings and for planning healthcare services (augmenting hospital beds, use of antivirals, and delivery of supplemental oxygen) in developing countries where access to healthcare is likely to improve in the next 5 to 10 years. Additionally, the morbidity and mortality data could contribute to future Global Burden of Disease estimates (especially in computing aetiology specific estimates of years of life lost).

5.2. Limitations

The data sources and the methodology used for estimating the disease burden have several limitations. Estimates are very variable within countries or regions and between regions. These variations could be partially attributable to variation in influenza epidemiology between study populations and yearly variations in influenza severity (Thompson et al., 2010). It was not possible to make global incidence estimates by type/subtype of influenza virus because of insufficient studies conducted in the same year with the same subtype and often mixed strains circulating. The limited data available indicate that influenza A has a higher incidence compared to influenza B. Indeed, the virulence and severity of disease is known to vary by the type/subtype of the influenza virus – influenza A (particularly H3N2 subtype) has been shown to result in higher morbidity and mortality than influenza B (Thompson et al., 2010, Johnson et al., 2009). However, the majority of the variation in the data presented in this study may be artefactual (a result of chance, potential bias and / or confounding) and therefore these limitations should be borne in mind while interpreting the results.

5.2.1. Incidence-based estimates

5.2.1.1. Study population and duration of study

The population at risk in the included studies varied from about 250 to 5.6 million children younger than 5 years. While the studies with population denominators less than thousand children were cohort studies in developing countries, the studies from industrialised countries were mostly retrospective studies using discharge diagnosis from hospital records and laboratory data, and had large denominator population. The individual incidence estimates in the included studies having a smaller population denominator are likely to have wider 95% confidence intervals, thus affecting the precision of the estimates.

Although all included studies had to satisfy the minimum eligibility criteria for study duration (12 consecutive months), the duration of included studies varied from one year to 25 years. The epidemiology of seasonal influenza virus suggests considerable variation in the severity of disease episodes from year to year. Therefore, any incidence estimate based on study duration of one year while indicative of the incidence in the given year, is unlikely to reflect the average disease burden associated with seasonal influenza. However, the incidence meta-estimates for developing and industrialised countries were based on 39 studies and thus

reflect the average incidence of seasonal influenza-associated ALRI rather than the estimate for an individual year.

5.2.1.2. Case ascertainment

These estimates are based on hospital-based studies using passive case ascertainment (wherein a child with ALRI is brought to a healthcare facility). Therefore, these incidence estimates are influenced by the healthcare seeking behaviour of the population and the admission practices / policies of the attending physician / hospital respectively. The estimates for industrialised countries (where access to healthcare and healthcare seeking behaviour are good and decisions for hospital admission are based on objective clinical criteria) are likely to reflect the true burden of severe disease. On the other hand, estimates for hospitalisations in resource-poor settings in developing countries are unlikely to be reflective of the true burden of severe disease because healthcare seeking behaviour is poor and access to healthcare is limited (Nokes et al., 2009, Sutanto et al., 2002). Previous studies in Kenya and the Gambia have shown two-fold to 10 fold decreases in hospital pneumonia admissions in areas farthest from the hospital (Nokes et al., 2009, Weber et al., 2002, Bigogo et al., 2010). Recent data from Bangladesh and Kenya have also shown a marked decrease in hospitalisation rates out with a 4 km radius from the hospital (Nair et al., 2013) (Figure 18). In one study, investigators attempted to reduce this distance decay effect through provision of reimbursement for travel costs; nonetheless about 25% of referred children did not attend the hospital (Nokes et al., 2009). Therefore, while these estimates are an underestimate of the severe disease due to influenza-associated ALRI, it is not possible to quantify the degree of underestimation. However, these estimates are indicative of the burden on hospital inpatient services in developing countries.

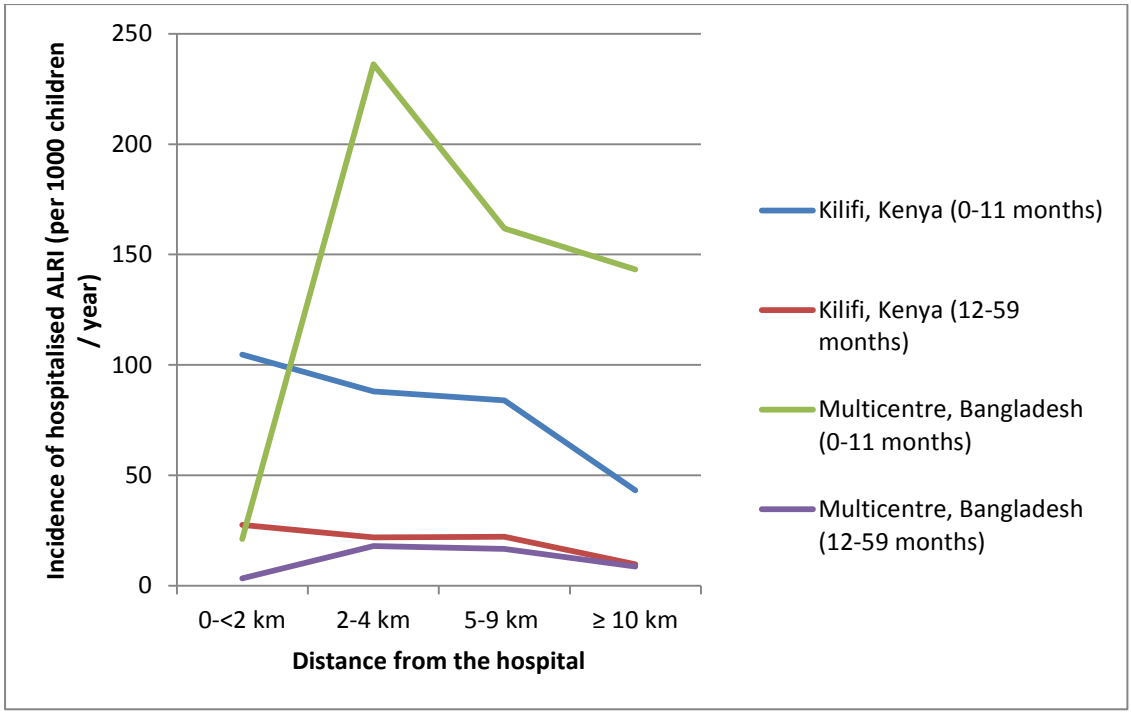

Figure 18: Variation in incidence (per 1000 children per year) of hospitalised ALRI in children younger than 5 years by distance from hospital

5.2.1.3. Case definition

The thirty nine included studies did not use the same case definition for hospitalised influenza-associated ALRI. The variability in case definitions was more in the case of developing countries. While six of the 21 studies from developing countries used a case definition of laboratory confirmed influenza in a child hospitalised for ALRI based on a physician's diagnosis, six studies required presence of lower chest wall indrawing in addition to a physician's diagnosis of ALRI, and the remaining nine studies required an additional criteria (like presence of WHO specified danger signs (Department of Child and Adolescent Health, 2005), or clinical or laboratory signs of acute infection). Similarly, in the case of industrialised countries too, the case definitions were variable– 10 of the 18 studies used laboratory confirmed influenza in a child hospitalised for ALRI based on a physician's diagnosis, six studies used a mixture of ICD codes (for influenza and pneumonia) and two studies required radiological confirmation of ALRI.

The absence of a standardised case definition resulting in substantial variability in case definitions in the included studies is likely to have contributed to some of the variation in the incidence estimates across different sites. However, this bias was attempted to be minimised

by encouraging sites contributing unpublished data to reanalyse their data using common case definitions. In spite of this, studies that have used a more stringent case definition are unlikely to have collected clinical specimens, and conducted diagnostic tests in children who did not fulfil their initial eligibility criteria and therefore reported lower estimates compared to those studies that used a more broad-based case definition.

5.2.1.4. Laboratory diagnosis

Five studies identified infection with influenza virus either by rapid tests such as EIA or immunofluorescence alone and 11 used them in combination with either PCR or viral culture. Immunofluorescence assays have shown variable and lower sensitivity and specificity compared to PCR which have very high sensitivity and specificity (Espy et al., 1986, Rawlinson et al., 2004, Stockton et al., 1998, Grijalva et al., 2007a, Yoo et al., 2007). It is not possible to estimate the overall effect of this bias as it depends on relative sensitivity and specificity of the individual assays, which were unknown for most studies. However, this has not resulted in a significant difference in the final estimates as a sensitivity analysis conducted using only PCR-based studies demonstrated consistency in the incidence estimates (Table 23).

Table 23: Results of a sensitivity analysis on the incidence of hospitalised influenza-associated ALRI in young children after including only PCR-based studies

	Children aged below 1 year	Children aged below 5 years
Developing countries		
Incidence rates after including only PCR-based studies *		
No. of studies	12	12
Incidence (per 1000 children per year)	3.1 (95% CI 1.9 to 5.0)	1.6 (95% CI 0.9 to 2.7)
Incidence rates from all studies satisfying eligibility criteria		
No. of studies	21	21
Incidence (per 1000 children per year)	2.7 (95% CI 1.8 to 4)	1.5 (95% CI 1 to 2.3)
Industrialised countries		
Incidence rates after including only PCR-based studies		
No. of studies	14	14
Incidence (per 1000 children per year)	2.1 (95% CI 1.6 to 2.9)	1.0 (95% CI 0.7 to 1.5)
Incidence rates from all studies satisfying eligibility criteria		
No. of studies	18	18
Incidence (per 1000 children per year)	2.4 (95% CI 1.7 to 3.2)	1.3 (95% CI 1 to 1.8)

* Includes studies where PCR was used in combination with viral culture

Thirteen of the 39 included studies collected clinical specimens for diagnostic assays using nasopharyngeal / nasal / throat swabs. Although, nasopharyngeal aspirate is considered to be the best specimen for detection of influenza viruses (Zambon, 1998), recent research has shown that specimens collected using the less invasive nasal swab / nasopharyngeal swab in combination with molecular diagnostic techniques like PCR and time-resolved fluoroimmunoassay (monoclonal antibodies) have a sensitivity of 91 to 92% compared to nasopharyngeal aspirates which are difficult to collect in low resource settings (Heikkinen et al., 2001, Lambert et al., 2008b). However, nasopharyngeal aspirates have been demonstrated to be more sensitive for detecting influenza B virus (Sung et al., 2008). Since available data from included studies demonstrate that influenza A was the predominantly circulating virus, use of nasopharyngeal/nasal swabs are unlikely to have resulted in a substantial difference in incidence estimates.

Many of the included studies have collected clinical specimens in a proportion of the eligible cases (i.e. systematically collected samples in only a proportion of eligible hospitalised ALRI cases). In other studies, even though the study protocol recommended collection of clinical specimens in all eligible cases, a proportion of eligible children were excluded for various reasons (Table 24). Although in both scenarios, the estimated number of hospitalised influenza positive ALRI cases has been adjusted by scaling for the proportion sampled (assuming that influenza positivity rate is similar in both groups), this is unlikely to be true and would have contributed to some bias in the estimates. If it is assumed that disease severity is correlated to influenza positivity, the hospitalised ALRI cases where clinical specimens were not collected (e.g. critically ill, died before sample collection, were intubated etc.) are more likely to be influenza positive, and would have thus resulted in an underestimation of the incidence estimates.

Table 24: Reasons (from three unpublished studies) for not collecting clinical specimens from all eligible hospitalised ALRI cases

Location (reference)	Study period	Proportion of eligible children with hospitalised for ALRI in who clinical specimens were not collected (n/N)	Reason
Manhiça district, Mozambique (Roca and colleagues, unpublished)	2006-2007	7.6% (67/874)	Admitted late at night or on weekends, no physical presentation of severity, critically ill or died before sample collection
Kilifi district, Kenya (Berkley and colleagues, unpublished)	2007	18% (163/922)	Child was critically ill, or was discharged before nasal wash was conducted
Santa Rosa, Guatemala (Lindblade and colleagues, unpublished)	2008	11.1%	Refused nasopharyngeal swab or were intubated

Nasopharyngeal carriage of a pathogen presents a major challenge while attributing a causal association in ALRI cases. Previous studies in the Gambia have shown that influenza virus can be isolated from asymptomatic children (Adegbola et al., 1994). However, recent well-designed case-control studies reveal that the proportion of asymptomatic children who are positive for influenza virus is very low (Berkley et al., 2010, Singleton et al., 2010). Nevertheless, disease burden estimates based solely on laboratory identification of influenza virus in a nasal / nasopharyngeal clinical specimen should be interpreted with caution. In this study, this may have resulted in overestimation of the true incidence of influenza-associated hospitalised ALRI. Ideally, identification of influenza virus in clinical specimens collected using lung aspiration could be used to confirm a causal association (Scott and Hall, 1999). Lung aspirates in combination with PCR significantly increases diagnostic yield in children with both bacterial as well as viral ALRIs (Carrol et al., 2011). However, for disease burden estimation, a simpler approach like vaccine probe studies such as those conducted for *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B (Lucero and Williams, 2005, Lucero et al., 2009, Gessner et al., 2005, Cutts et al., 2005, Madhi et al., 2005) is being advocated since an effective influenza vaccine is available. However, adopting this approach

would be challenging as the effectiveness of the influenza vaccine varies from year to year (depending on the circulating strain of circulating viruses) (Jefferson et al., 2012).

5.2.1.5. Methodological issues

5.2.1.5.1. Study period

There are two possible criticisms of the methodology used in this study. First, this study included only papers published since January 1995. This was done because studies prior to the latter half of 1990s primarily used serology or virus culture for diagnosis and results from the former are not really comparable with those from modern molecular techniques. The second and more important point is that the estimates for the year 2008 are based on data that spans a period of about 15 years (1 January 1995 to 31 October 2010). As has been already noted, there is substantial variability in the severity of influenza-associated ALRI from year to year in a given setting. The median period of the data included in this study is 2004. This method of estimating disease burden captures the underlying uncertainty in the true disease burden estimates, and is likely to reflect the seasonal influenza-associated hospitalised ALRI burden in 2008.

5.2.1.5.2. Data imputation

Only 24 of the 39 studies included for estimating the incidence of influenza-associated hospitalised ALRI reported data for the full age range (i.e. both for age 0 to 11 months as well as 0 to 59 months). For the remaining 15 studies missing data were imputed using median incidence rate ratio. In order to assess the validity of data after imputation, a sensitivity analysis was carried out by including only studies which had data for the full age range. The incidence rates for influenza-associated hospitalised ALRI (using data with and without imputation) for industrialised and developing countries were comparable for both infants (aged less than one year) and young children (aged less than five years). However, at the regional level, the incidence rates (from the two analyses) for infants in Americas were significantly different because 10 studies did not have data for the full age range (Table 25).

Table 25: Results of sensitivity analysis for incidence (per 1000 children per year) of influenza-associated hospitalised ALRI in young children using imputed and unimputed data

Region	Number of studies	Incidence of influenza-associated hospitalised ALRI in infants < 1 year (95% CI) per thousand children per year	Number of studies	Incidence of influenza-associated hospitalised ALRI in young children <5 years (95% CI) per thousand children per year
Analysis with data imputation				
Africa	6	2.3 (1.6 to 3.4)	6	1.0 (0.9 to 1.2)
Americas	16	2.5 (1.8 to 3.6)	16	1.2 (1.0 to 1.6)
Europe	6	1.9 (1.3 to 2.8)	6	1.1 (0.7 to 1.6)
South-east Asia	4	2.2 (0.7 to 6.8)	4	1.4 (0.4 to 5.6)
Western Pacific	7	3.6 (1.7 to 7.4)	7	2.1 (0.9 to 5.1)
Developing countries	20	2.8 (2.0 to 4.1)	20	1.5 (1.0 to 2.3)
Industrialised countries	19	2.3 (1.7 to 3.0)	19	1.2 (0.9 to 1.6)
Analysis without data imputation				
Africa	6	2.3 (1.6 to 3.4)	6	1.0 (0.9 to 1.2)
Americas	6	1.9 (1.1 to 3.1)	13	1.2 (0.8 to 1.9)
Europe	4	2.1 (1.7 to 2.6)	5	1.2 (0.9 to 1.6)
South-east Asia	2	2.3 (0.3 to 16.3)	3	1.5 (0.3 to 7.1)
Western Pacific	8	3.3 (1.7 to 6.4)	6	2.3 (0.9 to 6.0)
Developing countries	14	2.9 (1.9 to 4.4)	16	1.5 (0.9 to 2.3)
Industrialised countries	12	2.1 (1.5 to 2.8)	17	1.2 (0.9 to 1.8)

There are other overarching limitations related to methods employed in the study and are discussed later in section 5.2.4.

5.2.2. Prevalence-based estimates

5.2.2.1. Study population and duration of study

The population at risk in the studies included for estimating the incidence of hospitalised ALRI in young children varied from about 500 to about 48 million. While the studies with

population denominators less than thousand children were cohort studies, the larger studies from industrialised countries were mostly retrospective studies using discharge diagnosis from hospital records. The individual incidence estimates in the included studies having a smaller population denominator are likely to have wider 95% confidence intervals, thus affecting the precision of the estimates. Although all included studies had to satisfy the minimum eligibility criteria for study duration (12 consecutive months), the duration of included studies varied from one year to 25 years. The available data suggest considerable variation in the severity of ALRI episodes from year to year. Therefore, any incidence estimate based on study duration of one year while indicative of the incidence in the given year, is unlikely to reflect the average disease burden associated with hospitalised ALRI. However, the incidence meta-estimates for developing and industrialised countries were based on 85 studies (median year 2005) and thus reflect the average incidence of hospitalised ALRI rather than the estimate for an individual year.

5.2.2.2. Case ascertainment

These estimates are based on hospital-based studies using passive case ascertainment (wherein a child with ALRI is brought to a healthcare facility). Therefore, these incidence estimates are influenced by the healthcare seeking behaviour of the population and the admission practices / policies of the attending physician / hospital respectively. Since this study attempted to estimate the incidence of hospitalised ALRI in young children, and thereby the burden of ALRI on hospital inpatient services, rather than the (total) burden of severe ALRI, and all included studies had a well-defined catchment population, the ascertainment bias has been minimised.

5.2.2.3. Case definition

Estimates of hospitalised ALRI are very variable within and between countries and regions and across different study periods. The 85 included studies did not use the same (standard) case definition for hospitalised ALRI. The variability in case definitions was more in the case of developing countries. While 17 of the 61 studies from developing countries used a case definition of physician diagnosed ALRI, 33 studies used the WHO case definition of severe pneumonia (based on lower chest wall indrawing) (Department of Child and Adolescent Health, 2005), and four studies used either of these. Additionally, one study used a case definition based on more specific clinical signs and symptoms suggestive of acute infection, while six others used hospital discharge diagnosis. Similarly, in the case of industrialised

countries too, the case definitions were variable – nine of the 24 studies used a case definition of hospitalisation for ALRI based on a physician's diagnosis, 14 studies used a mixture of ICD codes (for pneumonia and bronchiolitis), and one study included only children with bronchiolitis.

The absence of a standardised case definition resulting in substantial variability in the case definitions in the included studies is likely to have contributed to some of the variation in the incidence estimates across different sites. However, this bias was attempted to be minimised by encouraging sites contributing unpublished data to reanalyse their data using common case definitions. In spite of this, studies that have used a more stringent case definition (excluding cases not fulfilling their stringent clinical criteria for inclusion) may not have included all the excluded cases during the re-analysis and therefore underestimated the true incidence of hospitalised ALRI. Estimates from developing and industrialised countries are not strictly comparable as case definitions in the former tend to be based on simpler clinical syndromic criteria with no requirement for results of investigations.

The case definitions employed by the 23 studies reporting the proportion of hospitalised ALRI cases in children positive for seasonal influenza were less variable. While 15 of the 19 studies from developing countries used a simple case definition of hospitalisation for ALRI (based on a physician's diagnosis), three required additional radiological confirmation, and one used the SARI case definition. Similarly, three of the four studies from industrialised countries used the simple case definition of hospitalised ALRI, while one used a mixture of ICD codes from hospital records.

5.2.2.4. Laboratory diagnosis

Similar issues relating to clinical specimens, and diagnostic assays (as discussed for the studies reporting incidence of influenza-associated hospitalised ALRI) were present in studies estimating the proportion of hospitalised ALRI cases positive for seasonal influenza. Only six of the 19 studies from developing countries used PCR-based assays and four used either viral culture alone or in combination with immunofluorescence assays. The meta-estimates of proportion of hospitalised ALRI cases positive for seasonal influenza were highest in PCR-based studies (Table 26).

Table 26: Sensitivity analysis (based on diagnostic assays) comparing the meta-estimates of the proportion of hospitalised ALRI cases positive for seasonal influenza in children younger than five years residing in developing countries

No. of studies	Meta-estimate of proportion (%) of hospitalised ALRI cases positive for seasonal influenza (95% CI)
PCR-based studies only	
6	7.8 (4.9 to 12.4)
PCR and viral culture-based studies only	
10	7.1 (5.1 to 9.9)
All eligible studies	
19	5.0 (3.6 to 7.0)

Thirteen of the 19 studies from developing countries used nasopharyngeal aspirates or nasal wash to collect clinical specimens while two others used these in combination with nasal / nasopharyngeal swabs. This is perhaps one of the reasons why the overall influenza positivity rate is consistent with what is seen from incidence-based studies (7.8 percent compared with 8.5 percent), even though the proportion of studies using PCR-based assays was higher in the incidence based studies (57% compared to 32% in prevalence-based studies).

Detailed data regarding the eligible cases where clinical specimens were not collected have not been provided in the included studies. Since the denominator in these cases are all children hospitalised for ALRI and fulfilling the case definition, it is assumed that clinical specimens were collected in all these cases. However, if certain children were excluded from specimen collection (a likely scenario) because they were very sick, or if the parents refused to provide consent or the child died before specimen collection, the resulting estimates would be biased, and if these cases were more likely to be influenza positive, then the estimated proportion is likely to be an underestimate.

5.2.2.5. Methodological issues

5.2.2.5.1. Data imputation

Only 43 of the 85 studies included for estimating the incidence of hospitalised ALRI in young children reported data for the full age range (i.e. both for age 0 to 11 months as well as

0 to 59 months). For the remaining 42 studies missing data were imputed using median incidence rate ratio. In order to assess the validity of data after imputation, a sensitivity analysis was carried out by including only studies which had data for the full age range. The incidence rates for hospitalised ALRI (using data with and without imputation) for industrialised and developing countries were comparable for young children (aged 0-59 months) (Table 27). However, the incidence rates were not comparable in infants (0-11 months) for the industrialised region (because 11 studies with missing data were excluded). For the same reason, the meta-estimates for Europe and South-east Asia were not comparable in infants.

Table 27: Results of sensitivity analysis for incidence (per 1000 children per year) of hospitalised ALRI in young children using imputed and unimputed data

Region	Number of studies	Incidence of hospitalised ALRI in infants < 1 year (95% CI) per thousand children per year	Number of studies	Incidence of hospitalised ALRI in young children <5 years (95% CI) per thousand children per year
Analysis with data imputation				
Africa	13	49.3 (30.4 to 79.8)	13	21.1(13.6 to 32.8)
Americas	18	38.7 (30.0 to 50.0)	18	17.4 (12.0 to 25.3)
Eastern Mediterranean	2	27.9 (14, 55.5)	2	12.1 (8.6 to 17.2)
Europe	14	14.2 (8.1, 25)	14	7.3 (4.6 to 11.6)
South-east Asia	13	49.8 (33.6 to 73.8)	13	18.6 (11.4 to 30.3)
Western Pacific	25	43 (32.3, 57.3)	25	17.3 (13.4 to 22.3)
Developing countries	61	48.6 (41.0 to 57.6)	61	18.9 (15.9 to 22.4)
Industrialised countries	24	19.1 (15.7 to 23.4)	24	9.6 (7.1 to 13.0)
Analysis without data imputation				
Africa	11	51.3 (28.6 to 92.1)	10	24.7 (14.7 to 41.2)
Americas	17	38.6 (29.7 to 50.2)	9	16.0 (10.1 to 25.5)
Eastern Mediterranean	2	27.9 (14.0 to 55.5)	2	12.1 (8.6 to 17.2)
Europe	5	17.7 (3.6 to 87.8)	8	5.7 (5.0 to 6.5)
South-east Asia	7	78.6 (73.0 to 83.6)	9	18.3 (8.4 to 40.0)
Western Pacific	9	47.6 (37.8 to 60.0)	24	16.8 (13.0 to 21.8)
Developing countries	38	54.5 (46.5 to 63.9)	48	18.7 (15.1 to 23.3)
Industrialised countries	13	42.5 (35 to 51.5)	14	8.3 (5.9 to 11.8)

5.2.3. Mortality estimates

5.2.3.1. Influenza-associated in-hospital case fatality

The in-hospital CFR meta-estimates for influenza-associated ALRI reported in this study are for a broad age range (0-59 months). There were insufficient data to report in-hospital CFR for influenza-associated ALRI for narrower age ranges (e.g. 0 to 11 months, or 0 to 23 months) having the highest incidence rates for influenza-associated hospitalised ALRI. Even for this broad age range, substantial uncertainty surrounds the in-hospital CFR estimates from developing countries. First, as has been pointed out earlier, many studies only obtained clinical specimens from and carried out diagnostic test in a random sample of the proportion of eligible cases. Some sites have reported that clinical specimens were not collected from a proportion of eligible children because they were either critically ill, or refused participation or were discharged or died before clinical specimens could be collected. The absence of clinical specimen collection in all children hospitalised for ALRI introduces a bias towards falsely low reported estimates because mortality tends to be higher in these groups. Second, although the in-hospital CFR has been estimated separately for broad developing and industrialised country categories, the degrees to which the included studies are representative of these broad categories are unknown. Though in this instance, it has been attempted to reduce the selection bias by combining the incidence of hospitalised cases with the in-hospital CFR data, the studies might be from settings with above average resources, and thus the reported in-hospital CFR would be an underestimate of the true CFR in hospital settings in developing countries. Finally, infection with influenza virus has been shown to predispose to bacterial infection, particularly pneumococcal pneumonia (Klugman et al., 2009, O'Brien et al., 2000, Zaman et al., 2008, McCullers, 2006, McCullers et al., 2010). Results from a nine-valent pneumococcal vaccine probe study in South Africa indicates that a minimum 45% of the cases with influenza-associated severe ALRI have co-infection with *Streptococcus pneumoniae* (Klugman et al., 2009). While bacterial infections are reported to have higher CFR (at least in developing country settings), the sensitivity of the diagnostic tests to identify bacterial infection remains poor (Sutanto et al., 2002, Isaacs, 1989, Lankinen et al., 1997). While attempting to fairly interpret childhood pneumonia deaths, it may be worthwhile to co-attribute mortality to both influenza and bacterial pneumonia in cases with influenza and bacterial co-infection.

This study documents a more than 8-fold difference in the in-hospital CFR meta-estimates for influenza-associated ALRI for the developing regions compared to the industrialised regions.

This could be attributable to epidemiological factors such as population immunity; circulation of *Streptococcus pneumoniae*; circulating type/subtype of influenza virus; clinical factors such as availability of oxygen, mechanical ventilation, antivirals, trained nursing staff; and access to care. The estimates based on in-hospital CFR have been regarded as the lower bound of the influenza-associated ALRI mortality estimates. There are two key reasons why this estimate should be considered as an underestimate. First, the estimates of influenza-associated hospitalised ALRI are likely to be an underestimate of the true burden of influenza-associated severe ALRI. Second, in-hospital CFRs from included studies cannot be regarded as representative of whole population groups. In the most resource poor settings, the true CFR for influenza-associated ALRI would be much higher than these reported estimates as the resources and quality of care in study hospitals are likely to above average.

On the other hand, it is possible that the true in-hospital influenza-associated ALRI mortality for 2008 is lower than what has been estimated here. Data available from published and unpublished studies demonstrate that there has been a general decrease in the in-hospital CFR for ALRI over the last decade (Figure 19). This is consistent with the reported decrease in childhood pneumonia mortality during this period (Liu et al., 2012). Since the in-hospital mortality for influenza-associated ALRI in 2008 has been based on in-hospital CFR data for a period ranging from 1996 to 2008 (median year 2003), the true in-hospital mortality for that year is perhaps lower than what has been estimated. However, the proportion of in-hospital ALRI mortality attributable to seasonal influenza is likely to be consistent with what has been estimated in this study. More significantly, these data demonstrate that 99% of influenza-associated ALRI mortality occurs in developing countries.

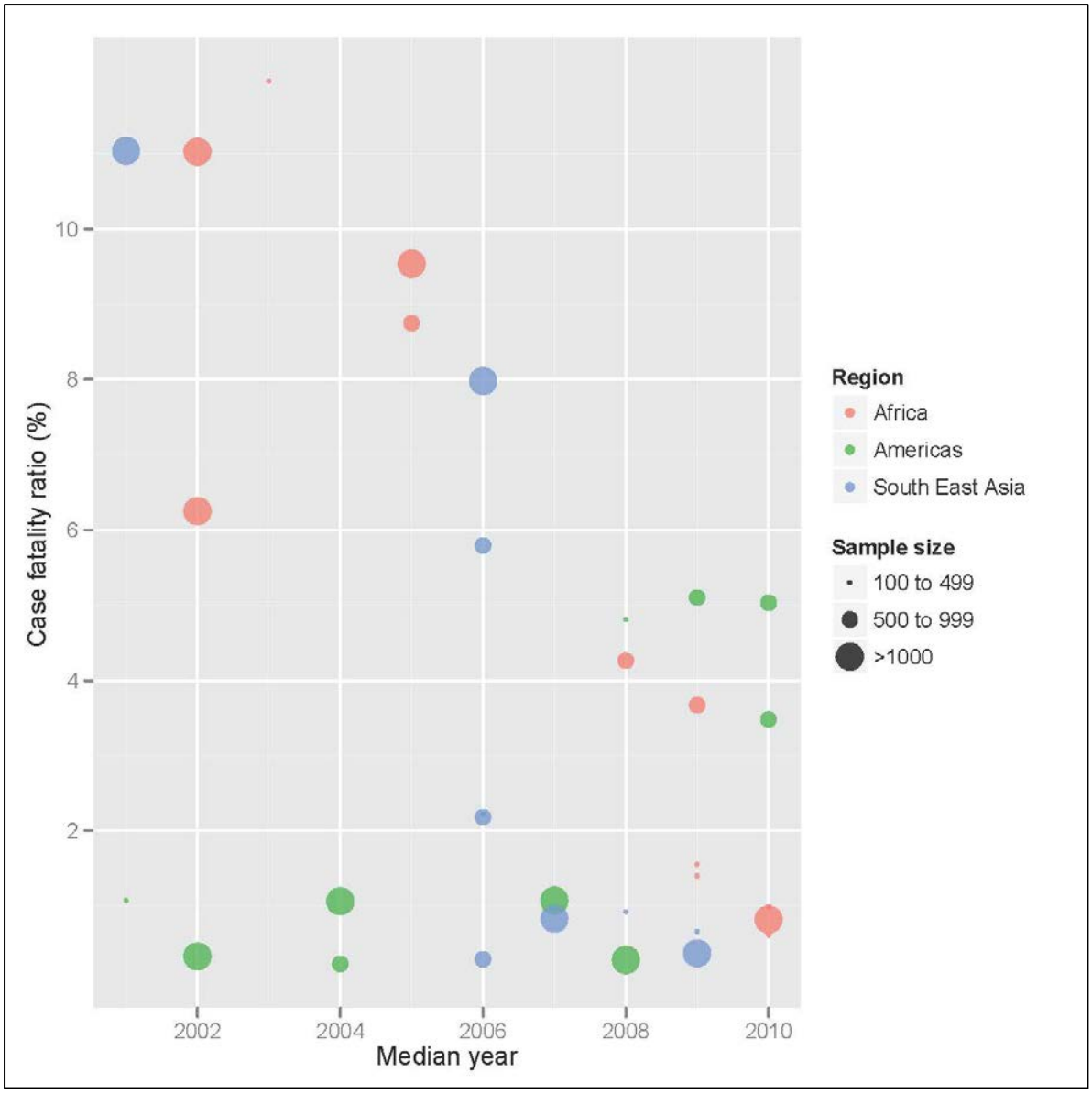

Figure 19: In-hospital case fatality ratio for young children with ALRI by WHO regions from 2000 to 2010

There were no data from developing countries to validate the estimated lower bound for influenza-associated ALRI mortality. However, in the case of industrialised countries, the estimated influenza-associated ALRI mortality for US (76 deaths) was consistent with that reported by Thompson and colleagues (92 deaths) for American children (aged 0-59 months) for 1992 to 1999 (Thompson et al., 2003).

5.2.3.2. Influenza-associated ALRI mortality in the community

This study utilised population-based data on cause of death in children not admitted to hospital, assigned by verbal autopsy, and concurrent seasonal influenza virus isolation in the

same population, to estimate the excess ALRI mortality during the "influenza season". This estimate has been considered as the upper bound of influenza-associated ALRI mortality in children. The site at Ballabgarh in North India is typical of most developing countries with high infant and child mortality, with majority of deaths occurring at home (Nongkynrih et al., 2003, AIIMS, 2010). The mortality rate is lower than many African countries and other Indian states but is higher than many other developing countries in South / South East Asia and Latin America. Due to paucity of data, data on deaths in community from this site have been used to predict the likely upper bound for influenza-associated ALRI mortality in developing region. Since the upper bound is based only on one study in a small rural population in one country, this method needs to be replicated in other settings. Additionally, although all excess ALRI mortality during the influenza season has been attributed to influenza, RSV is known to co-circulate during the influenza season (Zambon et al., 2001). The acute respiratory infections in which RSV and seasonal influenza are identified are clinically indistinguishable although influenza appears to result in more febrile illness (Bosis et al., 2005). Since RSV is a leading pathogen identified in cases with ALRI, it is important to identify the periods of RSV transmission while delineating the "influenza season". In the case of data from Ballabgarh, a random sample of about 10% of the clinical specimens for the period 2006-2008 was tested for RSV and it was observed that there was no overlap in the periods of peak activity for both viruses (Broor, personal communication). However, several other viral pathogens (e.g. parainfluenza virus and human metapneumovirus) causing ALRI have (unknown) seasonal patterns. These pathogens could, in some areas, account for as much as a third of the ALRI hospital admissions and may have a similar, if not higher, CFR to influenza (Foulongne et al., 2006, Madhi et al., 2007, Hamelin et al., 2004, Wolf et al., 2006, Nascimento-Carvalho et al., 2010). Also, unlike in Ballabgarh, in many developing countries, seasonal influenza and RSV are likely to co-circulate. Therefore, the estimated upper bound of influenza-associated ALRI mortality in children is likely to be an overestimate.

On the other hand, the assumption that no influenza mortality in young children occurs outside the "influenza season" is unlikely to be true in developing countries located in tropical and subtropical areas which have typically demonstrated a year round circulation of the virus with one or two peaks annually (Sam et al., 2010, Nicholson et al., 2006). Additionally, a substantial proportion of ALRI mortality in the three to four weeks after an infection with seasonal influenza virus may be the result of subsequent infection with a

bacterial pathogen (where influenza may have predisposed the child to bacterial infection) (McCullers, 2006, McCullers et al., 2010). Both these factors are likely to result in an under-estimation of the upper bound of influenza-associated mortality.

The estimated upper bound of influenza-associated ALRI mortality indicates that about 7% of all ALRI mortality in children younger than five years is associated with influenza. This estimate is consistent with the estimated proportion of influenza-associated ALRI mortality that occurs in hospitals (7.6 percent). More importantly, this indicates that about 81% (93095 [†]/ 114627) of all influenza-associated ALRI deaths in young children occur outside hospitals or health facilities. This finding is consistent with the recent estimate that only 19% of all ALRI deaths in young children occur in hospitals (Nair et al., 2013) and other published estimates (Sutanto et al., 2002, Sacarlal et al., 2009, Adazu et al., 2005).

5.2.4. Overarching limitations

5.2.4.1. Location of study sites

This study has utilised data from published literature and unpublished data available with the Influenza Study Group and the Severe ALRI Working Group to estimate the number of hospitalised influenza-associated ALRI cases in young children in the year 2008. The included studies span a 15 year period from 1995 to 2010. About 54 to 82% of included data are from developing countries. In spite of these efforts, there are large parts of the world for which no data are available (e.g. Russia, Central Asia, Middle East, and North Africa). Similarly, data on influenza-associated ALRI were scarce from mainland China. The only study from mainland China was identified in English language databases. To supplement data from mainland China, three Chinese language databases were extensively searched to identify studies reporting population-based data on incidence of influenza-associated ALRI in Chinese literature. Additionally, the Chinese Centre for Disease Control and Prevention was contacted to identify any unpublished data reporting incidence of influenza-associated ALRI in China. However, despite these efforts, no additional studies reporting incidence of influenza-associated ALRI in children younger than five years were identified. Chinese language databases could not be searched for identifying studies reporting proportion of hospitalised ALRI cases positive for seasonal influenza (as the services of a Chinese

[†] Estimated in-hospital deaths due to influenza associated ALRI= 21532. Therefore, the out-of hospital influenza-associated ALRI deaths= (114627-21532)= 93095

language researcher was no longer available). Although literature search in English language databases identified two studies in Chinese language, data from these studies could not be included in the meta-analysis as the two studies could not be translated using Google translator.

5.2.4.2. Methodological issues

5.2.4.2.1. Confidence intervals

There are two methodological issues related to confidence intervals for the results presented in this study. First, the 95% confidence intervals for the point estimates are asymmetric. This is because where possible, the 95% CIs for the included studies were calculated using Poisson distribution rather than binomial distribution (Kirkwood and Sterne, 2006). In the case of studies with small sample sizes, the 95% CI are likely to be asymmetric. Second and more importantly, the 95% confidence intervals of the meta-estimates are narrower than the conference intervals of the individual studies. It is known that meta-analyses appear to give results that are more precise and more conclusive than are unwarranted (Egger et al., 1998). The large number of subjects contributing to the meta-analysis will often lead to very narrow confidence intervals for effect estimate. This is because while the 95% CI of individual study represents the underlying sampling variability (random error), the meta-estimates represent an average value after combining the individual studies using different weights (assuming they all are measuring the same effect), and the 95% confidence interval represents the probability that the interval includes the true value (Henmi and Copas, 2010). Also it is crucial to remember that these endeavours do not account for the various biases across studies; rather they take account of only between-study variation in effect, or bias only under restrictive assumptions. When uncertainties about bias sources are included in the meta-analysis, the interval estimates will expand dramatically (Eddy et al., 1992, Greenland, 2005). While the sources of bias have been discussed qualitatively in this study (and the likely direction and scale have been discussed), it has not been possible to conduct a formal *bias analysis* (for quantitatively adjusting the estimates) because such analyses require data on quantitative assessment of systematic errors which are not available in published studies. In the absence of such data, either educated guesses can be made, which in the current scenario (absence of accepted convention regarding the specifications), leave the input judgements entirely to the analyst, thus opening avenues for manipulation to produce desired results; or data can be obtained from validation studies which may themselves be subject systematic errors beyond those present in the main studies (Greenland and Lash, 2008).

5.2.4.2.2. Random effects meta-analysis

Random effects model assumes a hypothetical random distribution of effects, thus incorporating real differences in effect in each study as well as sampling variability (chance). This generalisation more accurately reflects uncertainty about unaccounted for sources of variation in study results. However, the summary estimate obtained from a random effects model has no population specific interpretation. It does not correspond to an average effect in an actual population, but instead represents the mean of a distribution of effects across included studies (Greenland and O'Rourke, 2008). The random effects meta-analysis weights the studies by the inverse of the variance within studies as well as the between study variance. Thus, here the study weights are assigned with the goal of minimizing both sources of variance. The model gives proportionally greater weight to smaller studies than do fixed effects estimates. As a consequence, the random effects summaries will be more affected by biases that more strongly affect small studies (Thompson and Pocock, 1991, Poole and Greenland, 1999). If the number of studies is very small, as in the case of in-hospital CFR meta-estimates for influenza-associated ALRI (section 3.2.2.1), the estimate of the between studies variance will have poor precision (Borenstein et al., 2009). In such situations, while the random effects model is still the most appropriate, there are a few alternatives− a simple descriptive analysis without reporting summary effect; or a fixed-effects analysis; or a Bayesian meta-analysis- none of which have been accepted as standard.

5.2.4.2.3. Study specific factors

The hospitalisation for influenza-associated ALRI is likely to be influenced by environmental factors relating to the study setting (like altitude, rainfall, humidity, and temperature); study design (such as median year of study, mean cohort size, duration of study, duration of surveillance); and cultural factors and access to healthcare. Rudan and colleagues in their paper on the incidence of clinical pneumonia in young children assessed the association between these factors and the incidence of clinical pneumonia and made several adjustments in their final estimates (Rudan et al., 2004). However, this study has not undertaken any formal assessment of association between the above-mentioned factors and incidence of influenza-associated hospitalised ALRI and made post-hoc assessment for the reasons given below:

- Since the environmental factors relate to the true incidence at the study site, they do not warrant adjustment. This approach is consistent with the findings and conclusions by Rudan and colleagues (Rudan et al., 2004).

- The majority of the factors relating to study design were accounted for either through the inclusion criteria− limiting the included studies to those published after 1995 (rather than 1960 onwards as was done by Rudan), duration of study, duration of influenza surveillance etc.− or through the use of random effects meta-analysis (rather than a median estimate approach used by Rudan).

- Since this study aims to estimate the burden of paediatric seasonal influenza-associated ALRI on hospital inpatient services, rather than the overall disease burden, it was not necessary to adjust the incidence estimates based on cultural factors (determining healthcare seeking behaviour) and access to healthcare.

5.2.4.2.4. Confounding by RSV

Clinically, RSV-associated ALRI are indistinguishable from influenza-associated ALRI although influenza appears to result in more febrile illness (Bosis et al., 2005). As discussed earlier, the peak transmission periods of RSV and seasonal influenza are known to overlap in many settings. The estimates reported in this study have not been adjusted for confounding by RSV activity. This is because clinical signs and symptoms have not been used as the sole criteria to define hospitalised influenza-associated ALRI cases. Laboratory confirmation using valid diagnostic test has been used to attribute the illness to influenza (as was done in the estimates for RSV-associated ALRI). Thus, RSV is unlikely to be a confounder for incidence estimates for influenza-associated hospitalised ALRI. Some studies in the past (Izurieta et al., 2000, Mullooly et al., 2007, Thompson et al., 2003) which have analysed both RSV and influenza together have tried to adjust for the co-circulation using mathematical models. However, these studies were not estimating true rates based on virologically confirmed cases. Since this study only includes hospitalised ALRI cases with laboratory confirmed diagnosis of seasonal influenza, the estimated rates reflect the true rates and thus do not require statistical adjustments.

5.2.5. Disease burden estimation using SARI surveillance data

The manual developed for estimating disease burden associated with seasonal influenza is targeted at developing countries and uses certain broad assumptions in order to assist WHO

member states for estimating their national seasonal influenza-associated SARI disease burden. There are several key limitations to the methods outlined in the manual:

- The manual focuses primarily on morbidity. To estimate mortality, only one approach (i.e. in-hospital case fatality ratio) has been used. Data from vital registration are scarce in resource poor settings at which this manual is targeted. However, in certain middle-income countries (e.g. Russia, Chile, Argentina and Venezuela), vital registration of deaths is more than 90% complete (Rudan et al., 2005). In these countries, modelling approaches using cause of death data from vital registration and data on influenza activity from virological surveillance can be used to estimate the influenza-associated mortality.
- The manual proposes a rather simplistic method of estimating the catchment population for a SARI sentinel site. While this method is likely to suffice for a stable population where care seeking for pneumonia (preference for healthcare provider) does not change over time, this is unlikely to be true, in situations where the population is mobile, and healthcare provider preference changes from year to year and season to season (depending on accessibility issues).
- There are various sources of uncertainty in the disease burden estimates generated using surveillance data. The manual only deals with one of the sources of uncertainty – random error due to variation in sampling – and provides the reader with the methods for calculating the 95% confidence intervals. Although the other sources of uncertainty (biases) are discussed qualitatively, in the absence of quantification of this uncertainty, the average reader may be led to believe that the true uncertainty in the estimates have been captured in a standard 95% confidence interval.
- For estimating disease burden at the national level, the manual describes combining data from different SARI sentinel sites that are representative of the national population using a median approach. This method, though simple, is very crude and does not capture the variation within and between the various SARI sentinel sites included in the analysis.
- The methods outlined in the manual assume that vaccination for seasonal influenza is non-existent in the low and middle-income countries which are targeted in the manual. However, while this may be the case at present, this assumption is unlikely to be true in the future. Therefore, ideally the manual should have outlined techniques

for estimating disease burden after adjusting for the coverage of seasonal influenza vaccines.

- The manual only deals with disease burden estimation using laboratory confirmed influenza. The methods outlined in the manual do not incorporate data from serologically determined influenza incidence (e.g. studies like FluWatch) (Research Department of Infection and Population Health, 2012).
- The manual focuses on disease burden due to influenza-associated SARI. While this would reflect the burden on hospital inpatient services, the majority of the disease burden associated with seasonal influenza is at the milder end of the spectrum (Nair et al., 2011). The mild influenza like illnesses and the non-severe influenza-associated ALRI that do not result in hospitalisation nevertheless pose a significant burden on hospital / clinic outpatient services and result in significant economic costs due to workplace absences, reduce productivity and school closures (during outbreaks / pandemics).
- The manual focuses solely on the "medical burden" due to seasonal influenza-associated SARI. While the data on hospitalisation is useful for planning purposes, such data coupled with costs associated with hospitalisation make a powerful argument for introducing interventions against seasonal influenza (e.g. vaccines, anti-virals etc.). Therefore, the manual should have included a toolkit for economic analysis for seasonal influenza-associated SARI.
- The manual focuses solely on seasonal influenza. While the burden of seasonal influenza in itself is an important public health problem, it cannot be viewed in isolation against the larger burden associated with respiratory viruses. Most countries presently use modern molecular techniques which can identify multiple respiratory pathogens from a single sample (e.g. multiplex PCR). Ideally, the manual should have been expanded to include disease burden estimation for other major respiratory viruses.
- The manual does not provide details on how to compare the seasonal influenza-associated disease SARI burden estimates with the estimates for other diseases.
- The manual assumes that the average reader is trained in basic epidemiology and therefore would not require any formal training. This is unlikely to be true in most developing countries settings and therefore this manual should be accompanied by a trainer's manual.

5.3. Public health impact of influenza

Using data from hospital-based studies with a clear population denominator and an incidence rate-based approach, it was estimated that in 2008 approximately 911,000 (95% CI 617,000 to 1.4 million) hospitalisations due to influenza-associated ALRI occurred in children under the age of five years. Using data from studies (without a known population denominator) reporting the proportion of hospitalised ALRI cases positive for seasonal influenza using laboratory diagnosis and the global and regional estimates of hospitalised all-cause ALRI cases, it was estimated that in the same year, about 772,000 (95% CI 343,000 to 1.8 million) hospitalisations due to influenza-associated ALRI occurred in children younger than five years. Thus, seasonal influenza was associated with about 8% of all hospitalised ALRI in children younger than 5 years in 2008.

In-hospital CFRs in influenza-associated ALRI cases were utilised to estimate the lower boundary of ALRI deaths in children younger than five years that would be attributable to influenza. These data indicate that about 21530 (95% CI 3960 to 55700) in-hospital ALRI deaths (translating to about 7.6% of all in-hospital ALRI deaths) occurred in children younger than five years with laboratory confirmed influenza. Only one site reported cause of death data (in children not admitted to hospital), assigned by verbal autopsy and concurrent isolation of influenza virus in the same population for a period of three consecutive years. Using these data and a comparative model, it was estimated that globally 114,450 (95% CI 20,950 to 296,450) deaths in under-five children (about 7.2% of all childhood ALRI deaths in 2008) could be attributed to influenza-associated ALRI. These findings are summarised in Figure 20 and demonstrate the internal consistency of the results derived using different approaches and independent data sources. Approximately 92% of hospitalisations due to influenza-associated ALRI and 99% of influenza-associated ALRI deaths occurred in developing countries.

Available data indicate that the incidence of influenza-associated hospitalised ALRI was highest in infants, especially those in the first six months of life. There is substantial variability in the incidence of influenza-associated hospitalised ALRI between regions and from year to year within a country / or region. This variability can be explained partly by the circulating type/subtype of the influenza virus- with influenza A(H3N2) resulting in more severe disease. Secondary bacterial pneumonia commonly caused by *Streptococcus pneumoniae* and *Staphylococcus aureus* is a frequent complication of influenza-associated

ALRI (Klugman et al., 2009, Reed et al., 2009, van der Sluijs et al., 2010, Foulongne et al., 2006). Insufficient data were available to estimate the burden of co-infections (especially with a bacterial pathogen) in children hospitalised for ALRI.

These estimates indicate that seasonal influenza is the second most common viral pathogen identified in young children with ALRI when placed in context with disease burden estimates for other respiratory pathogens (*Streptococcus pneumoniae, Haemophilus influenzae* type B, and RSV) that are associated with 49% of severe episodes likely to result in hospitalisation and 61% of deaths (O'Brien et al., 2009, Watt et al., 2009, Nair et al., 2010). However, these estimates are not directly comparable because:

- The estimates for the bacterial pathogens were based on a small number of vaccine probe studies and were for the year 2000.
- The RSV estimates were based on a similar approach (though with fewer data points), and were for the year 2005.

Nonetheless, these estimates indicate that seasonal influenza is an important contributor to childhood pneumonia morbidity and mortality.

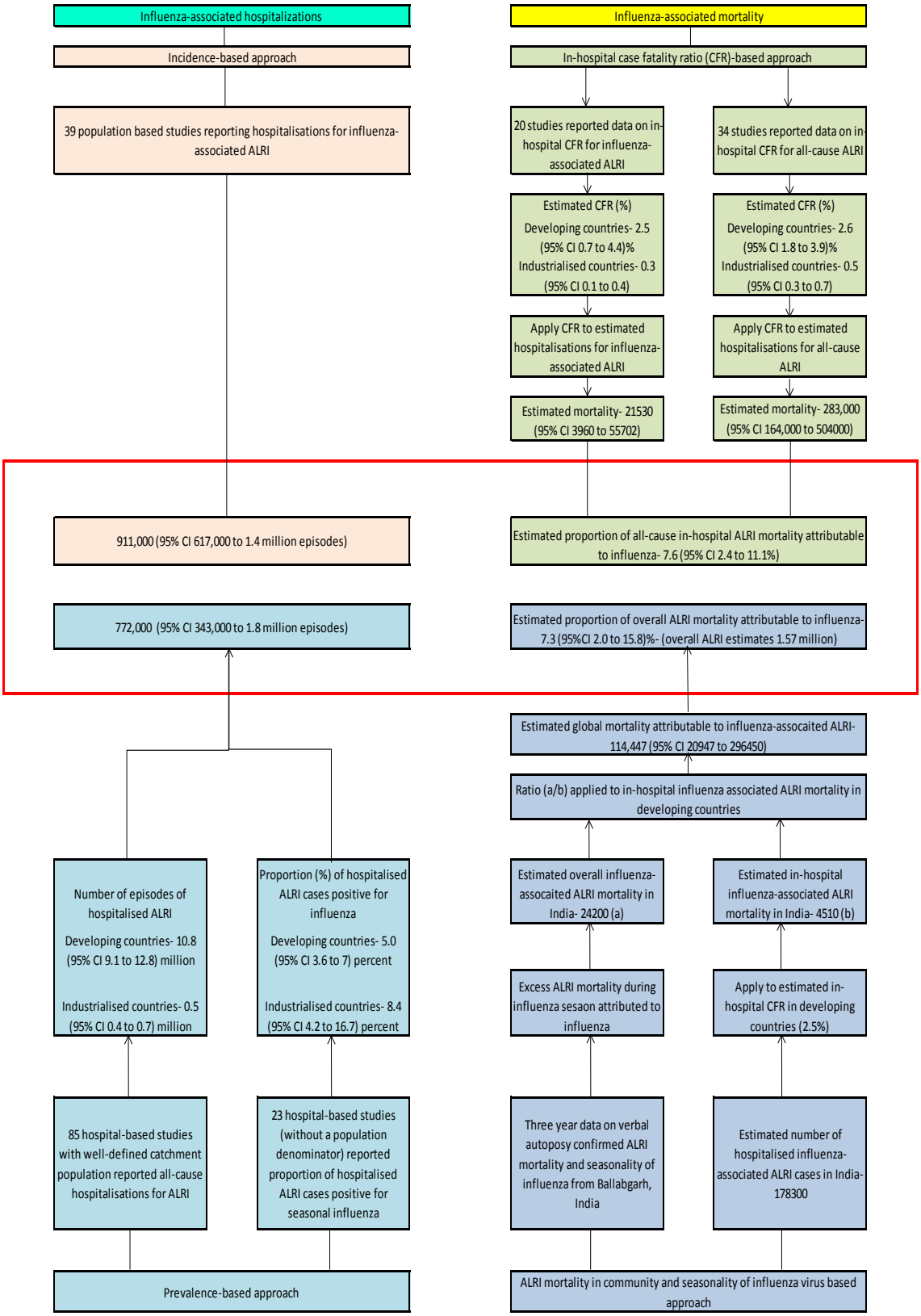

Figure 20: Hospitalizations and mortality due to influenza-associated ALRI in children aged 0-59 months estimated using two different approaches and independent data sources

5.4. Implications for vaccination policies and strategies using existing vaccines

There are two broad categories of existing influenza vaccines- trivalent inactivated vaccines (TIV) and live attenuated influenza vaccines (LAIV) - both containing two influenza A strains and one influenza B strain. In order to ensure optimal vaccine efficacy against prevailing strains of influenza virus, the antigenic composition of the influenza vaccine is revised annually (once each for the Northern and Southern hemispheres) depending on the virological data obtained from the WHO global influenza surveillance and response system (GISRS).

The majority of currently available TIVs are split-virion vaccines, sometimes adjuvanted to enhance the immunogenicity (Waddington et al., 2010, Vesikari et al., 2009). Only unadjuvanted TIVs are currently licensed for use in children older than six months of age. Antibody responses to TIV are related to the age of the infant with decreased antibody responses noted stepwise in children 6 to 23 months of age (Walter et al., 2010). A recent Cochrane review reported that TIVs have an efficacy of 59 (95% CI 41 to 71) percent, and vaccine effectiveness of 36 (95% CI 24 to 46) percent in children aged 24-59 months (Jefferson et al., 2012). However, there were insufficient data to estimate the efficacy and effectiveness in children aged 6 to 23 months. TIVs are in general considered to be safe in young children and although transient local reactions at the injection site may occur frequently, no evidence of important medically attended adverse events following immunisation have been noted (Neuzil et al., 2001, Vellozzi et al., 2009, France et al., 2004).

TIVs are the only vaccines licensed for immunisation against influenza in pregnant women. It has been demonstrated previously that maternal antibodies transferred transplacentally confer protection against influenza during the neonates' first months of life (Englund et al., 1993, Glezen, 2003, Reuman et al., 1987, Puck et al., 1980). However, there are no vaccine effectiveness studies in pregnant women that have used laboratory confirmed influenza outcomes in vaccine recipients (Ortiz et al., 2011). Results from three vaccine trials in pregnant women have demonstrated that laboratory confirmed influenza virus infections are lower among young infants whose mothers received the TIV (Eick et al., 2011, Zaman et al., 2008, Poehling et al., 2011). Randomised controlled trials in pregnant women in USA and Bangladesh have not reported any significant adverse outcomes in the pregnant women or their offspring (from foetal period through infancy) (Englund et al., 1993, Zaman et al.,

2008). Therefore, maternal vaccination against influenza using platforms like the maternal and neonatal tetanus (MNT) elimination initiative which exist in all resource poor countries has been recommended for protecting young infants (Ortiz et al., 2012). Currently, there are several large trials in low resource settings (e.g. Nepal, Mali and South Africa) assessing the impact of maternal vaccination against influenza, both on the pregnant woman as well as the young infant (Adegbola et al., 2012).

LAIVs are currently licenced for use in in healthy adults and children above two years of age in North America, European Union, South Korea, Hong Kong, Macau and Israel. Jefferson and colleagues in their recent review report that LAIVs have a good vaccine efficacy (80; 95% CI 68 to 87) percent in children aged more than 2 years (Jefferson et al., 2012). A meta-analyses comparing the immunogenicity of intranasally administered LAIV with egg-based TIV in children (6 months to 17 years old) demonstrated the superior efficacy of the LAIV compared to TIV (Rhorer et al., 2009). Apart from transient febrile reactions in less than one percent of children immediately after immunisation, no serious adverse events following immunisation with LAIVs have been reported (Rudenko et al., 1996). Presently, none of the vaccine trials using TIV or LAIV have used laboratory confirmed influenza-associated pneumonia as an endpoint. In order to bridge this gap, four large vaccine trials (in Bangladesh, India, Kenya and Senegal) funded by US CDC are currently underway that are using influenza-associated SARI as an endpoint (Centres for Disease Control and Prevention, 2012).

This body of work demonstrates that seasonal influenza is a major pathogen identified in young children hospitalised for acute lower respiratory infections. The majority of the disease burden occurs in children younger than two years of age (Nair et al., 2011). The burden of influenza-associated ALRI on hospital inpatient services is disproportionately higher in infants particularly those in the first six months of life. Therefore, young children (aged less than five years), particularly young infants (aged below six months) are one of the high risk groups for immunisation against seasonal influenza. Brooks suggests that integration of seasonal influenza vaccine into routine immunisation programmes (along with the vaccines against bacterial pneumonia) remains the key to decreasing childhood pneumonia morbidity and mortality (Brooks, 2009). The WHO now recommends that immunising pregnant women against influenza should be accorded the highest priority (World Health Organization, 2012). Universal immunisation of children aged 6-59 months using existing influenza vaccines has

also been recommended as a priority intervention (World Health Organization, 2012). However, implementing such a recommendation in resource limited setting is likely to be challenging and contestable for the following reasons:

i. the existing public health infrastructure in developing countries is already overburdened and routine administration of seasonal influenza vaccine by EPI or maternal and child health (MCH) services would most likely be opposed by policy makers and health workers
ii. recent evidence demonstrates that repeated immunization with seasonal influenza vaccine may not be effective (Ohmit et al., 2013). This could be due partly to antigenic interference and partly to confounding (Treanor and Szilagyi, 2013)
iii. a recent randomised controlled trial in children aged 6-15 years has demonstrated that children immunized with TIV were more likely to be infected with non-influenza respiratory virus compared to the placebo group (Cowling et al., 2012)
iv. recent data from Europe suggest that in the elderly and clinical high risk groups, the vaccine effectiveness is lower than that estimated by Osterholm and colleagues (Nicoll and Sprenger, 2013)

The burden of seasonal influenza is under recognised in developing countries owing to paucity of good quality data on the role of influenza in childhood pneumonia (Brooks et al., 2010). In the absence of such data, uptake of the seasonal influenza vaccine has been poor (especially in high influenza burden developing countries). This is linked to the limited vaccine production capacity in low resource settings and ultimately impairs the much needed surge in influenza vaccine production capacity during pandemics. The WHO now considers production and uptake of seasonal influenza vaccines as an integral part of pandemic influenza preparedness planning (World Health Organisation, 2011). To this end, there is an urgent need to increase the production and uptake of seasonal influenza vaccine especially in high burden settings in low income countries. National governments in developing countries with high disease burden of influenza-associated ALRI need to recognise the role of seasonal influenza as a major contributor to childhood ALRI morbidity and mortality. In order to meet the demands for a surge in vaccine production during pandemics, technology transfer and establishment of regional centres for vaccine manufacture in resource poor settings have already been incorporated as part of the Global Action Plan (GAP) for influenza vaccines (World Health Organisation, 2011). However, national level disease burden estimates using SARI sentinel surveillance data would assist national policy makers and health programme

partners in identifying risk groups, estimating cost effectiveness, so as to make an informed decision regarding introducing influenza vaccines into their immunisation programmes.

5.5. Proposals for improving future estimates

The current body of work has identified several gaps in data which need to be addressed in future studies estimating the disease burden due to influenza-associated respiratory infections:

- The estimates of hospitalisations and mortality due to influenza-associated ALRI are limited by the geographical representation of study sites. There are certain areas of the world from where no data were available (e.g., North Africa, Middle East, Central Asia and Russia). Limited data were available from large countries like India and China that contribute to about 40% of the global population. Rudan and colleagues demonstrated a similar gap in data (in the year 2000) for ALRI morbidity and mortality (Rudan et al., 2005). While funding future studies, funding agencies need to ensure geographical representation of study sites so that the findings from similar meta-analyses are more generalisable.
- Although, several studies have reported a higher incidence rate for hospitalised ALRI in young children, existing studies on influenza-associated ALRI do not report gender-based incidence estimates. Future studies need to consider reporting gender-specific data for morbidity and mortality.
- The majority of the existing studies do not report incidence rates and case fatality ratios for narrow age ranges (e.g. 0-5 months, 6-11 months, 12-23 months). In order to precisely identify the age groups at the highest risk (for influenza related morbidity and mortality), and make informed policy decisions for targeted interventions (particularly maternal vaccination to protect young infants), there is an urgent need to report data by narrow age bands at least in the first two years of life.
- Post-mortem diagnostic testing for influenza in children with acute lower respiratory infections who die in hospital before clinical specimens can be collected for diagnostic testing would assist in estimating the true in-hospital CFR for influenza-associated ALRI.
- In order to precisely estimate the mortality due to influenza-associated ALRI in young children, studies where good quality mortality data (either from vital registration or confirmation using verbal autopsy) along with concurrent isolation of respiratory

viruses (like RSV, seasonal influenza, human meta-pneumovirus, and parainfluenza virus) in the same population need to be carefully planned and implemented.

- In order to estimate disease burden due to influenza-associated ALRI in young children, vaccine probe studies (using a similar approach as was done for estimating the disease burden for *Streptococcus pneumoniae* and *Haemophilus influenzae* type B) should be considered. Such studies would help estimate disease burden due to non severe illnesses as well.
- Studies included in this meta-analysis did not report data on hypoxaemia in children hospitalised for ALRI and positive for influenza. Hypoxaemia has been shown to be an important predictor of mortality in children with severe pneumonia (Djelantik, 2003, Onyango et al., 1993, Duke et al., 2001). Availability of data on hypoxaemia as a specific risk factor for influenza-associated ALRI mortality would assist in advocacy and planning for pulse oximeters and oxygen concentrators in hospitals in resource constrained settings (Dobson et al., 1996, Duke et al., 2008).
- With the introduction and scaling up of pneumococcal conjugate vaccines (PCVs), future studies should record and report influenza incidence separately in PCV recipients and PCV recipients immunised against influenza.
- There are scarce data regarding co-infections with other viruses and bacteria in children hospitalised for influenza-associated ALRI. As newer molecular techniques capable of identifying multiple pathogens (like TAC) become available, well-designed case-control studies in combination with sero-epidemiology are likely to inform disease burden estimates (Laurie et al., 2012).
- There are scarce data on the milder influenza-associated respiratory infections that do not result in hospitalisation (i.e. influenza like illness and non-severe influenza-associated ALRI). Although per capita hospitalisations present a higher burden on healthcare systems, the economic burden resulting from workplace absences, loss of productivity and school closures (during outbreaks) due to the milder infections should not be underestimated. Population-based studies to estimate the incidence and costs related to non-severe influenza-associated respiratory infections should be considered perhaps as an extension to hospital-based studies in a well-defined catchment population.

5.6. Implementation of the disease burden manual

The generic guidelines to estimate disease burden associated with seasonal influenza using data from SARI sentinel surveillance has been prepared and the final draft is now being reviewed by the WHO for final clearance. While introducing this manual to member states, it would need to be emphasised that this manual is an adjunct to the "WHO interim global epidemiological surveillance standards for influenza" (WHO Global Influenza Programme, 2012) and that member states need to ensure availability of quality data conforming to at least the minimum requirements for undertaking disease burden estimation. The revised WHO surveillance guidelines provide detailed guidance on selection of appropriate sentinel sites for SARI surveillance. Although ideally, data from at least 3 to 5 years from multiple sites are required for robust disease burden estimates, at a minimum, the following data (for the age groups specified in the manual) must be available from at least one sentinel site for a continuous period of 12 months:

- total number of new SARI cases admitted to the sentinel site (by month)
- total number of new SARI cases where clinical specimens were collected for virological diagnosis (by month)
- number of new SARI cases positive for influenza (by month)

The experience from the inter-country meeting of the WHO Eastern Mediterranean Region in Marrakech in August 2012 demonstrates that the quality of SARI sentinel surveillance is highly variable within the region. While some countries like Egypt, Oman, Jordan and Iran have good quality SARI surveillance data, SARI sentinel surveillance is virtually non-existent in countries like Somalia, Sudan and Afghanistan. This is likely to be the scenario in most other developing country regions.

Since this is the first attempt to use sentinel surveillance data to generate disease burden estimates, it is expected that many of the steps which in theory appear to be very simple might be challenging in resource constrained settings. Therefore, the disease burden manual must now be evaluated in practice in different low and middle income countries before the final widespread adoption of the methods proposed in the manual. Initially, the countries chosen for introduction of the manual (evaluation phase) will require support in the form of training and supervision by technical experts trained in using the tool. Disease burden estimation using the methods outlined in the manual will require adequate support from academia, policymakers and healthcare planners at the national level. This is only possible

with repeated advocacy with academia and policymakers during the initial phase so as to ensure support for such a resource-intensive exercise. The disease burden estimates generated using the methods outlined in the manual would require validation against estimates from research studies (both published and on-going). There are numerous countries where the US CDC is supporting SARI surveillance through their IEIP field sites or collaborative cooperative agreements. Estimates from other SARI sentinel sites in the same country can be validated against the estimates from the IEIP study sites. Validation against routine data would be more challenging as countries with good routine data (e.g. USA, Australia and Western Europe) are not the targeted end-users of the manual. However, the results would need to be interpreted with caution- influenza disease burden can vary substantially from site to site within a country in any given year. During the evaluation phase, it is important to document carefully the best practices and challenges faced while implementing the tools outlined in the manual so that appropriate revisions can be made in the future versions and subsequent users can learn from the experience of previous users.

Chapter 6. Conclusions

This body of work demonstrates that influenza-associated ALRI confers substantial burden on hospital inpatient services, with approximately 1 (95% CI 0.6 to 1.4) million episodes of influenza-associated hospitalised ALRI (accounting for about 8 (95% CI 5.3 to 12.4) percent of all hospitalised ALRI) in children younger than five years in 2008. This study also demonstrates that about 7.6 (95% CI 2.4 to 11.1) percent of all childhood in-hospital ALRI mortality and about 7.3 (95% CI 2.0 to 15.8) percent of all ALRI deaths in young children are associated with seasonal influenza. Nonetheless, the evidence to support valid and precise estimates of global influenza-associated ALRI mortality is sparse and of low quality.

Research investment to gather further data is clearly needed. There are large gaps in data on influenza-associated ALRI hospitalizations from many regions of the world (particularly the Middle East, North Africa, Central Asia and Eastern Europe including Russia). Development and consistent application of standardised case definitions and study protocols (at least regionally) would make an important contribution towards addressing gaps in the data and substantially improving these estimates. The evidence base could be improved by a three pronged strategy. First, more research studies need to be initiated in low income countries (especially those in Africa and West Asia). Second, data systems in middle income countries (e.g. Brazil) can be strengthened by appropriate investments in hospital and other routine health information systems. Third, further evaluation of the WHO "Manual for Estimating Disease Burden Associated with Seasonal Influenza in a Population" through coordinated assessments in a variety of country settings should contribute towards standardising the case definition and data collection tools for improved disease burden estimates in the future. The disease burden estimates thus generated would require validation against estimates from research studies in the same country / region. Mortality estimates can be improved by gathering influenza and other respiratory viral pathogens isolation data from ALRI patients in sites where demographic surveillance records community-based pneumonia mortality. Further large-scale unselected case series reporting age specific in-hospital CFRs from many well described clinical settings in developing countries and large-scale post-mortem studies of ALRI cases that include investigation of seasonal influenza virus as a possible cause would also substantially improve the evidence base for the mortality estimate.

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Appendices

A1. Ethical Approval

A2. Glossary

AIIMS – All India Institute of Medical Sciences

ALRI– Acute Lower Respiratory Infections

AMP – Agence de Médicine Préventive

AOM – Acute Otitis Media

ARI – Acute Respiratory Infections

CDC – Centers for Disease Control and Prevention

CFR – case fatality ratio

CI– confidence interval

DFA – Direct immunofluorescence

DSS – Demographic Surveillance Site

EIA – Enzyme-linked Immunoassay

GISRS – Global Influenza Surveillance and Response System

HA – Hemagglutinin

HAART- Highly Active Antiretroviral Treatment

HAI – haemagglutination inhibition

HIV – Human Immunodeficiency Virus

HUS – Healthcare Utilisation Survey

ICD – International statistical classification of diseases and health related problems

ICU – Intensive Care Unit

IEIP – International Emerging Infections Program

IFA – Indirect immunofluorescence

ILI – Influenza like illness

IMCI – Integrated Management of Childhood Illness

IRR – Incidence Rate Ratio

LAIV – Live Attenuated Influenza Vaccines

MOH – Ministry of Health

NA – Neuraminidase

NIC – National Influenza Centre

PCR – Polymerase Chain Reaction

POC – point of care

PRISMA – preferred reporting items for systematic reviews and meta-analysis

RFP – Request for Proposals

RSV – Respiratory Syncytial Virus

SARI – Severe Acute Respiratory Infections

SAWG – Severe ALRI Working Group

TAC – Taqman Array Card

TAP – Technical Advisory Panel

TIV – Trivalent Inactivated Vaccines

URI – Upper Respiratory Infections

WBC – white blood cells

WHO – World Health Organization

A3. Search strategy to identify studies reporting influenza-associated ALRI hospitalizations in young children

Medline (Ovid)

1. exp Influenza, Human/
2. exp Influenzavirus B/ or exp Influenzavirus A/ or exp Influenzavirus C/
3. *Influenza Vaccines/ or *Influenza A virus/ or *Influenza, Human/ or *Influenza A Virus, H1N1 Subtype/
4. exp Bronchiolitis/ or exp Bronchiolitis, Viral/
5. exp Respiratory Tract Diseases/
6. exp Respiratory Tract Infections/ or acute respiratory infections.mp. or Influenza, Human/
7. exp Pneumonia, Viral/ or *Pneumonia/ or acute lower respiratory infections.mp.
8. exp Incidence/
9. exp Prevalence/
10. exp Morbidity/
11. exp Child Mortality/ or exp Infant Mortality/ or *Hospital Mortality/ or exp Mortality/
12. exp Death/ or exp "Cause of Death"/
13. burden.mp.
14. (1 or 2 or 3) and (4 or 5 or 6 or 7) and (8 or 9 or 10 or 11 or 12 or 13)
15. limit 14 to (humans and yr="1995 -Current" and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)"))

Embase

1. exp Influenza virus A/ or exp influenza/ or exp Influenza virus A H3N2/ or exp Influenza virus/ or exp Influenza virus A H1N1/ or exp Influenza virus B/
2. exp respiratory tract infection/
3. exp lower respiratory tract infection/
4. exp virus pneumonia/ or exp pneumonia/
5. exp bronchiolitis/ or exp viral bronchiolitis/
6. exp incidence/
7. exp prevalence/
8. exp morbidity/
9. exp mortality/ or exp childhood mortality/ or exp infant mortality/
10. exp death/ or exp child death/
11. burden.mp.
12. 1 and (2 or 3 or 4 or 5) and (6 or 7 or 8 or 9 or 10 or 11)
13. limit 12 to (human and yr="1995 -Current" and (infant or preschool child <1 to 6 years>))

Global Health

1. exp influenza A/ or exp Influenza A virus/ or exp Influenza B virus/ or exp influenza viruses/ or exp swine influenza A viruses/ or exp swine influenza viruses/ or exp influenza B/ or exp influenza/
2. (respiratory diseases or lower respiratory tract infections).sh.
3. exp pneumonia/
4. bronchiolitis.mp.

5. exp incidence/
6. burden.mp.
7. exp morbidity/

8. exp infant mortality/ or exp mortality/
9. exp death/ or exp "causes of death"/
10. 1 and (2 or 3 or 4) and (5 or 6 or 7 or 8 or 9)
11. limit 10 to yr="1995 -Current"

CINAHL

TI Influenza
OR
TI Influenza virus$
AND
TI acute respiratory infection
AND
TI children
Limiters: 1995-2010; infants: 1 to 23 months

WHOLIS

TI Influenza
AND
TI acute respiratory infection
AND
TI children
Publication year: 1995-2010

Web of Science

Title= (Influenza) AND Title= (Acute Respiratory Infections) OR Title= (Pneumonia) AND Topic=(Children)
Time span= 1995-2010

LILACS, IndMed and SIGLE

Influenza
AND
Children

A4. Search strategy to identify studies reporting ALRI hospitalizations in young children

MEDLINE
1. exp Pneumonia/
2. exp Respiratory Tract Infections/ or acute lower respiratory infections.mp.
3. acute respiratory infection$.mp.
4. lower respiratory infection$.mp.
5. exp Bronchiolitis/ or Bronchiolitis, Viral/
6. Pneumococcal Vaccines/ or Haemophilus Vaccines/
7. *Zinc/
8. Vitamin A/
9. exp Incidence/
10. disease burden.mp.
11. exp Morbidity/
12. 1 or 2 or 3 or 4 or 5
13. 6 or 7 or 8
14. 1 and 13
15. 9 or 10 or 11
16. 12 or 14
17. 15 and 16
18. limit 17 to (yr="1990 -Current" and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)") and humans)

EMBASE
1. exp respiratory tract infection/ or exp lower respiratory tract infection/ or acute lower respiratory tract infection$.mp. or exp pneumonia/
2. lower respiratory infection$.mp.
3. acute lower respiratory infection$.mp.
4. exp BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
5. exp Pneumococcus vaccine/
6. exp Haemophilus influenzae type b vaccine/
7. *ZINC/
8. *alpha tocopherol/ or Vitamin A.mp.
9. exp INCIDENCE/
10. disease burden.mp.
11. exp MORBIDITY/
12. 1 or 2 or 3 or 4
13. 5 or 6 or 7 or 8
14. 1 and 13
15. 9 or 10 or 11
16. 12 or 14
17. 15 and 16
18. limit 17 to (human and yr="1990 -Current" and (infant or preschool child <1 to 6 years>))

GLOBAL HEALTH
1. (pneumonia or lower respiratory tract infections).sh.
2. acute respiratory infection$.mp.
3. exp bronchiolitis/
4. vaccines.sh.

5. (retinol or zinc).sh.
6. exp incidence/
7. disease burden.mp. or morbidity.sh.
8. exp children/
9. 1 or 2 or 3
10. 4 or 5
11. 9 and 10
12. 6 or 7
13. 9 or 11
14. 12 and 13
15. 8 and 14
16. limit 15 to yr="1990 -Current"

CINAHL
TI Pneumonia
OR
TI Community Acquired Pneumonia
OR
TI Pneumonia Virus$
OR
TI Pneumonia bacteria$
OR
TI bronchiolitis
OR
TI Acute Lower Respiratory Infection.
AND
TI Children
Limiters: 1990-2012; infants: 1 to 23 months & Child, Preschool 2-5 years

WHO LIS
Title "Pneumonia" OR title "Community acquired pneumonia" OR title "bacterial pneumonia" OR title "viral pneumonia" OR title "acute lower respiratory infection" AND title "children"

LILACS
Pneumonia [Title words] or Community Acquired Pneumonia [Title words] and Children [Title words]

IndMED
(Pneumonia) OR (Community acquired pneumonia) AND (Children)
Web of Knowledge
Title=(Pneumonia) OR Title=(acute lower respiratory infection*) AND Title=(child*)
Timespan=1990-2012

SIGLE
Pneumonia AND Child*

A5. Calculations for adjusting the reported incidence of hospitalised ALRI for the year 2002 based on prevalence of paediatric HIV (<5 years) and access to HAART in 2008

Reported IR of hospitalised ALRI in all <5 year children (HIV pos and neg) in 2002, $I_{sev(2002)}$ = 3565 per 100,000
Prevalence of HIV in <5 year children in Soweto in 2002, $Prev_{2002}$= 5.5% (Madhi S, personal communication)
IR of hospitalised ALRI in HIV neg (I_{nsev})= 2566 per 100,000
IR of hospitalised ALRI in HIV pos (I_{psev})= 16724 per 100,000
$I_{sev(2002)} = I_{psev} + I_{nsev}$ ----------(1)

Prevalence of HIV in <5 year children (p_1) in Soweto in 2008, p_1 = 3.5% (Madhi S, personal communication)
Thus, IR of overall hospitalised ALRI adjusting for HIV prevalence in 2008, $I_{unadjsev(2008)}$
$= [I_{psev} \times p_1] + [I_{nsev} \times (1-p_1)]$
$= I_{punadjsev(2008)} + I_{nsev(2008)}$
$=[16724 \times 0.035] + [2566 \times 0.965]$
= 585.34 +2476.19 = 3061.53
Now $I_{punadjsev(2008)}$ is a combination of IR in those who receive HAART and those who don't
Proportion of access to HAART in Soweto in 2002, $P_{art(2002)}$ = 9%
Let us assume that risk of hospitalised ALRI in those who receive HAART= same as in HIV negative
Risk of hospitalised ALRI in HIV positive (with HAART) = X_1
Risk of hospitalised ALRI in HIV positive (without HAART) = X_2
Incidence of hospitalised ALRI in HIV positive, $I_{punadjsev(2008)}$
$=585.34= (9*X_1) + (91*X_2)$ ----------(2)
The risk of hospitalised ALRI in HIV positive compared to HIV negative in placebo group = I_{psev}/I_{nsev} = 6.5
Thus, X_2/X_1= 6.5
Substituting these in equation (2)
$I_{punadjsev(2008)} =585.34= 9X_1 + 591.5X_1 = 600.5X1$
Thus, X_1= 0.97
And X_2= 6.31

Proportion of access to HAART in Soweto in 2008= 75%
Substituting these values in equation (2)
$I_{padjsev(2008)} = 75*0.97+25*6.31$
=72.75+157.75 =230.5 ----------(3)

Substitutiting this value in equation (1)
$I_{sev(2008)} = I_{padjsev(2008)} + I_{nsev(2008)}$
$=2476.19+230.5$
= 2706.7
Incidence of hospitalised ALRI in 2008 after adjusting for HIV prevalence and HAART access = 2706.7 per 100,000 person years

A6. Questionnaire to assess perceived gaps in and needs for a manual to estimate influenza disease burden associated with seasonal influenza in low and middle income countries

WHO Project to Develop a Manual for Estimating Influenza Disease Burden

Dear Sir/ Madam,

The WHO Global Influenza Program is currently developing a manual on how to use existing surveillance data to produce disease burden estimates for influenza in WHO Member States. This manual will target healthcare planners and decision-makers of WHO Member States, particularly in those states with limited resources. The manual will aim to provide easy to use methods and techniques to estimate burden of severe human influenza-related respiratory disease using existing surveillance data. It would be useful in a wide range of settings using different types of available data and is aimed at public health professionals with basic epidemiological training. We aim to prepare a manual which is user friendly and responsive to the needs of the end user.

We would appreciate if you could please take out some of your valuable time to give your considered opinion on the topics we propose to include in this manual. We will use your feedback for developing the manual and will be pleased to share with you the draft and final version of the manual for comments. We will also formally acknowledge your contributions towards the development of the manual.

Thanking you,

With warm regards,

Dr. Harish Nair

Professor Harry Campbell

Centre for Population Health Sciences,
The University of Edinburgh,
Medical School, Teviot Place,
Edinburgh EH8 9AG

Influenza Disease Burden Manual Questionnaire

I. Personal details:

1. Country

2. What is your job title or position?

3. What is your professional qualification?

4. How many years have you been working in influenza / infectious disease surveillance?

Period	Tick where applicable
Less than 1 yr	
1 - 3 yrs	
3 - 6 ys	
6 – 10 yrs	
More than 10 yrs	

II. Your perspective regarding a manual to estimate influenza disease burden

Please answer the following questions briefly so that we can understand the perspectives of the potential target end-users of the manual.

1. Which division(s) in the Ministry of Health in your country is responsible for the surveillance and control of influenza?

2. Do you think seasonal influenza is an important public health problem in your country?

3. What data sources can you think of which could contribute to influenza burden estimation in your country? (*Please circle appropriate options and give details of any other sources*)

a) Population based data from sentinel sites conducting influenza surveillance

b) Data (from secondary or tertiary care hospitals) on hospitalised children with ALRI in whom influenza virus has been identified and a denominator population (for the hospital catchment area) can be estimated using health utilization surveys

c) Hospital data on proportion of children hospitalised for ALRI who are positive for influenza virus but no denominator population for the hospital catchment area can be estimated

d) Population-based data from areas under demographic surveillance which are testing for influenza virus in children presenting with influenza like illness (ILI) and severe acute respiratory infection (SARI)

e) Population-based data from cohort studies which are testing for influenza virus in children presenting with ILI and SARI

f) Other- please specify

g) Other- please specify

h) Other- please specify

4. Influenza surveillance data

(i). What type of influenza surveillance data you currently have?

(ii). What do you currently do with these data?

5. What in your opinion are the gaps in the capacities to do disease burden estimation in your setting / country? (E.g. lack of relevant data, lack of influenza testing capacity, shortage of trained manpower, lack of data management capacity, lack of political commitment to support this work, etc.)

6. In the context of your country, how useful do you think would be a manual which would provide general guidelines for influenza disease burden estimation? (*Please circle appropriate option and give reason why you think this*)
   a. essential b. very useful c. useful d. somewhat useful e. not useful f. can't say

7. What do you think would be the most useful aspects or elements of the manual in your national setting?

Please find below a draft table of contents for the manual for your perusal.

Table of contents (draft)

Looking at the proposed table of contents, could you please answer the following questions specifically in relation to your country?

8. Do you think this manual will be relevant in your country specific situation? Yes / No. Please justify your answer with suitable reasons

9. Who do you think this manual should primarily be aimed at?

10. Can you think of any other end-users of this manual in your country?

11. Do you think that adding a simple spread-sheet based model to help individual countries develop and triangulate country estimates (based on different data sources and approaches) would be useful tool in this manual?

12. Based on the table of contents, do you think the end-users will require training prior to using the manual?

13. If yes, what do you think will be the approximate number of persons who will need to be trained in your country so that the manual can be used routinely for influenza burden estimation?

Please consider some other questions regarding development of the manual.

14. We intend to desk-top pilot the manual in at least a couple of low and middle income countries before finalizing it. How useful do you think this would be and would you be interested in participating in this exercise? (*Please circle most appropriate option and give reasons*)
    a. essential b. very useful c. useful d. somewhat useful e. not useful f. can't say

15. Do you think that the manual would require being field tested before being adopted globally? Would you be interested in participating in this exercise?

III. General comment on the content of the manual

Attached is a draft table of contents for the manual for your perusal.

Please tick whether you think the following sections of the manual are:

	Essential	**Useful to include**	**Uncertain about need to include**	**Should not be included**
Background				
Rationale and need for influenza burden estimate				
Meaning of disease burden (definitions and descriptions of various ways to describe burden)				
Description of target audience				
Identifying the various sources of data for influenza				
Critical review of data for				

	Essential	**Useful to include**	**Uncertain about need to include**	**Should not be included**
quality and relevance				
Selecting appropriate data sources				
Mapping case definitions / data to appropriate ICD codes to aid interpretation of data				
Adjusting for incomplete data (accounting for sampling variation)				
Utilizing data from health utilization surveys to improve				

	Essential	**Useful to include**	**Uncertain about need to include**	**Should not be included**
burden estimates				
Adjusting for incomplete data on denominator population				
Estimating incidence, number of new episodes and mortality range in a calendar year				
Delineating influenza season				
Expressing a confidence range for estimates				
Carrying out a plausibility check with other available				

	Essential	**Useful to include**	**Uncertain about need to include**	**Should not be included**
data				
Looking at time trends over the years				
Presenting the data in an appropriate format for local decision makers				
Considering strategies to make appropriate use of these data in health services planning and priority setting				
Taking actions to promote local ownership of these data				
Encouraging data sharing				

	Essential	**Useful to include**	**Uncertain about need to include**	**Should not be included**
with neighbouring countries to compare influenza burden				
How seasonal patterns of influenza relate to seasonal patterns in ALRI hospital admission and how to interpret these findings				

IV. Detailed comments

We would appreciate your detailed comments on any of the sections which are listed here (e.g. what details you might think will be more relevant in your context, which sections may be redundant etc.). Additionally, if you feel any aspect relating to influenza burden estimation has been omitted please let us know.

Many thanks for taking the time to complete the questionnaire. Please return the questionnaire to:

Harish.Nair@ed.ac.uk or Essers@who.int

A7. List of publications by the author related to this thesis

1. Nair, H., Brooks, W. A., Katz, M., Roca, A., Berkley, J. A., Madhi, S. A., Simmerman, J. M., Gordon, A., Sato, M., Howie, S., et al. 2011. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet, 378, 1917-30.
2. Nair, H., Nokes, D., Gessner, B., Dherani, M., Madhi, S., Singleton, R., O'Brien, K., Roca, A., Wright, P., Bruce, N., et al. 2010. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet, 375, 1545-55.
3. Nair, H., Simoes, E. A., Rudan, I., Gessner, B. D., Azziz-Baumgartner, E., Zhang, J. S., Feikin, D. R., Mackenzie, G. A., Moisi, J. C., Roca, A., et al. 2013. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet.

A8. Copy of published / in press articles by author related to this thesis

A9. Copy of the "Manual for Estimating Disease Burden Associated with Seasonal Influenza in a Population"